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A.M.A. ARCHIVES OF

OPHTHALMOLOGY

The Position of Rest During Anesthesia and Sleep
Goodwin M. Breinin

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The Uveal Tract
Joseph A. C. Wadsworth

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CORNEAL CONTACT LENSES—THE FACTS

There is a great lack of accurate information on corneal contact lenses. Irrespective of their shortcomings, there exists today an increasing demand for them. Therefore, it would seem important to discuss them factually—both as to patient comfort (or discomfort) and potential corneal injury. We shall discuss only those people who wear corneal contact lenses (or micro lenses*) for cosmetic reasons. These views are based on the observation of several thousand cases and, although not necessarily infallible, should be representative.

We have found that most people can learn to wear corneal contacts, although the period of adjustment varies anywhere from three weeks to three months. In general, the successful patient is one who has a strong enough desire to wear contacts to cooperate completely during the period of adjustment and final fitting. A great deal of the adjustment has to be made by the patient, of course, who must accept the idea, as well as the fact, of having a foreign body on the eye—the awareness, not the discomfort. The final wearing time varies considerably, but the average is about eight hours. Even so—nearly 15% of the patients discontinue wearing their lenses after they have become adjusted to them.

The subject of potential corneal damage is a difficult one which can be judged only by what has not happened; we have never had nor seen a patient with a permanently damaged cornea as a result of wearing corneal contact lenses, although there have been many cases of superficial staining of the cornea.

We understand that it is possible to injure the cornea by extended wearing of ill-fitting lenses, although such a lens would be so very uncomfortable that a patient would normally remove it immediately. Further, using fluorescein and black light, an experienced technician can determine quite accurately how much pressure is on the cornea and what change must be made in the lens to reduce it. Since corneal lenses have been in general use only since 1949, there is as yet little indication of what effect their continued use over a period of twenty or more years will mean.

* The micro lens is the newer, thinner and smaller adaptation of the corneal lens. It averages 9-10 mm. in diameter compared to 10.5-12 mm. for the corneal lens.

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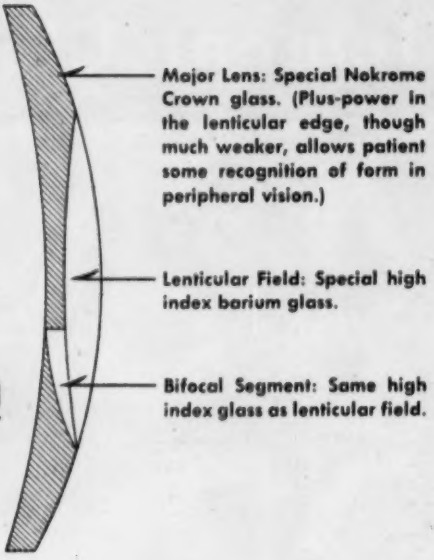
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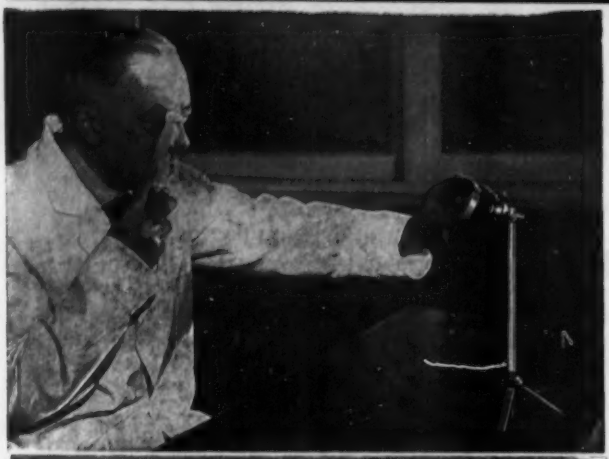

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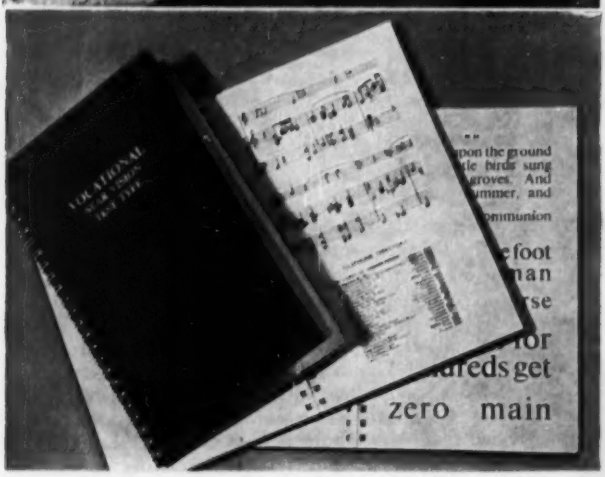

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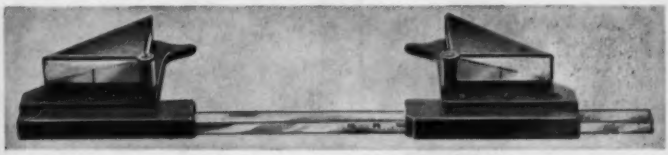

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A.M.A. ARCHIVES OF
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The Position of Rest During Anesthesia and Sleep

Electromyographic Observations

GOODWIN M. BREININ, M.D., New York

Considerable interest attaches to the position of the eyes during anesthesia and sleep. Reported observations have been conflicting.[1] During anesthesia different degrees of vergence have been noted, both vertical and horizontal, as well as roving motions during the induction. In surgical anesthesia the movements cease, and during the asphyxial stage a convergent depressed position may be assumed. A similar behavior may be noted during sleep.[2]

It is frequently observed that esotropia disappears during anesthesia, with straight eyes or divergence taking its place. This finding differentiates a purely innervational from an anatomic or mechanical strabismus and may trap the uninitiated into minimizing the necessary surgery.

Electromyography casts light upon the peculiar innervation during anesthesia and sleep. Operative procedures were carried out in a shielded room. The electromyographic technique has been previously reported.[3] Electro-oculography also was carried out with use of capacitance-coupled preamplifiers with a time constant of 0.5 second. Skin electrodes were affixed at the inner and outer canthi.

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A. Anesthesia

1. *General Anesthesia.*—During induction with thiopental (Pentothal) anesthesia in a patient with intermittent exotropia the innervation to the horizontal recti rapidly decreased (Fig. 1*A*, *B*). When the surgical plane was reached, all innervation was obtunded (Fig. 1*C*, 2*A*). The eyes occupied a moderately divergent position. As the level of anesthesia lightened, individual motor units appeared, which promptly disappeared when the plane of anesthesia was deepened. It was interesting to observe that the audio amplifier monitoring of the muscle discharge proved an excellent guide to the level of anesthesia. On hearing the popping of units in the loud speaker the anesthesiologist could maintain the depth without recourse to other signs. Peripheral skeletal muscle, which is electrically silent at rest, obviously could not provide such a guide. (I am not suggesting that this is a clinically feasible monitoring technique.)

(The response of extraocular muscle to intravenous succinylcholine was observed and is the subject of a separate report.[4] Ocular muscle of man and the cat is stimulated into brief firing by this drug, whereas peripheral muscle undergoes paralysis. The ocular muscle discharge in man, however, is blocked by deep anesthesia.)

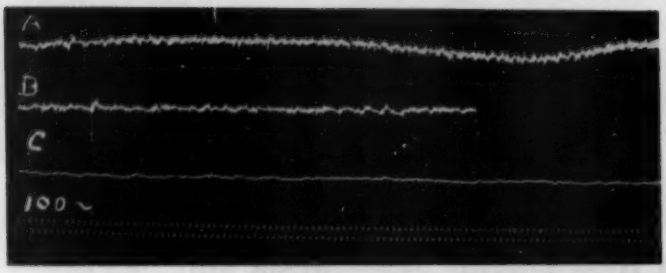

Fig. 1. — Electromyogram of the lateral rectus—general anesthesia. *A*, before anesthesia. *B*, several minutes after thiopental. *C*, surgical plane.

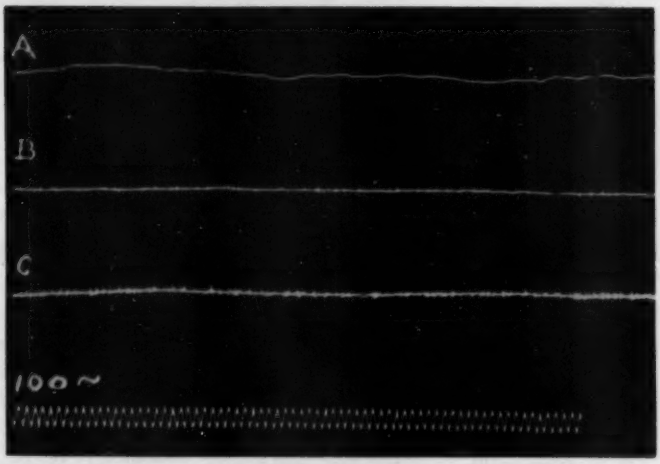

Fig. 2. — Electromyogram of lateral rectus—recovery from anesthesia. *A*, surgical plane. *B*, faint potentials as level lightened. *C*, recruitment returning; shortly after return to full preanesthetic level.

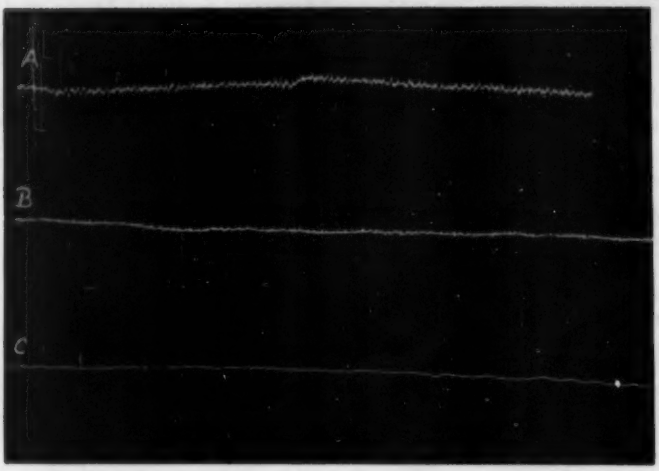

Fig. 3. — Electromyogram of lateral rectus—retrobulbar procaine anesthesia. *A*, before anesthetic was given. *B*, several minutes after injection. *C*, complete electrical silence in five minutes.

At the time of recovery from the anesthetic agent spontaneous recruitment appeared (Fig. 2*B*, *C*).

2. *Local Anesthesia.*—The efficacy of local or retrobulbar injections of procaine was readily assessed by the electrical response of the extraocular muscles. There was a progressive disappearance of motor units and decrease of amplitude, until the muscle became electrically silent (Fig. 3). This

rapid symmetrical response reflects the anatomic-pharmacologic uniformity and low innervation ratio of extraocular muscle. The same uniformity is noted in the response of extraocular muscle to excitatory as well as inhibitory drugs.[5]

B. Sleep

Electromyography was performed upon the horizontal recti of a rather phlegmatic person who was able to fall into a deep sleep despite the presence of the electrodes. This patient had spontaneous end-position nystagmus and exotropia during consciousness. A simultaneous electro-oculogram (EOG) was taken to record the horizontal movements of the eye.

During the light dozing phase very irregular discharges and bursts of potentials appeared (Fig. 4*C*). An interesting run of duplex (Fig. 4*A*) and single motor units (Fig. 5*B*, *C*) occurred at intervals, as well as rhythmic trains of potentials (Fig. 5*A*). During what appeared to be lightening of sleep induced by particularly cacophonous snores, a single burst of potentials occurred, accompanied by a movement of the globe, as shown by the EOG, Figure 5*B*. When the subject lapsed into deep sleep, the discharges decreased until brief intervals of electrical silence prevailed, for no more than one to two minutes at a time (Fig. 4*B*).

The electro-oculogram showed that rhythmic trains of discharges were each accom-

Fig. 4. — Electromyogram of medial rectus—in sleep. *A*, upper tracing, myogram, showing coupled units; lower tracing, EOG, showing no eye movement. *B*, deep sleep, electrical silence. *C*, light sleep, irregular bursts and runs of units on awakening turning into trains and then into normal discharge pattern.

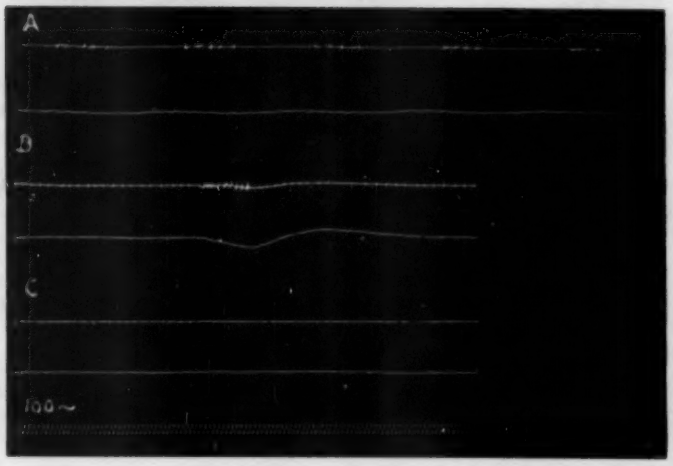

Fig. 5. — Electromyogram of medial rectus—in sleep. *A*, upper tracing, rhythmic trains of potentials; lower tracing, undulation of EOG, indicating eye movement with each train. *B*, upper, single unit discharge with one burst eliciting a movement of the globe; lower, EOG, showing deflection caused by innervation. *C*, upper, single unit discharges; lower, EOG, no movement.

panied by a slight movement of the globe, despite the low frequency and amplitude of these potentials (Fig. 5*A*).

As the subject slowly awakened, the discharges gradually increased up to the presleep level.

Comment

The position assumed by the eyes during surgical anesthesia is devoid of innervation. It is clear that this position is dictated by anatomical-mechanical factors — bony, fascial, and muscular—and represents the anatomical position of rest. It is, then, the basic position which is modified by numberless innervational factors during consciousness. If this basic position is one of divergence, then a basic stress toward divergence must underlie whatever position the eyes assume in consciousness. It opposes esodeviation and facilitates exodeviation. The frequency of divergence under surgical anesthesia supports the concept of a basic anatomical divergence, to which, in exotropia, may be added innervational divergence.

This basic exoposition also underlies esotropia and predisposes to the exodeviation of surgical over-correction or decreased esoinnervation, however induced. The existence of anatomic convergence would, of course, work in the opposite sense.

Summary

Electromyography during general and local anesthesia reveals a rapid loss of motor units until complete electrical silence results.

The implications of the innervation-free position of rest during anesthesia are discussed.

The EMG during sleep reveals intermittent irregular runs of units and rhythmic discharges, with brief intervals of electrical silence.

Simultaneous electromyography and electro-oculography enable detailed analysis of the innervation and its motor effects to be made.

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Central Retinal Artery Occlusion Associated with Cryoglobulinemia

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Cryoglobulinemia, a condition in which a protein or group of proteins in the blood precipitate on exposure to cold, may be associated with retinal vascular changes. This paper reviews the present knowledge of cryoglobulinemia and presents the eye findings which were present in one of three patients with cryoglobulinemia seen at the Veterans Administration Hospital in Philadelphia.

In 1933, Wintrobe and Buell described a cold-precipitable globulin. Others repeated this observation, but not until 1947 was the term cryoglobulin used.[4,7,13,16,22,49] Lerner and Watson, in 1947, while studying the blood serums of 121 patients suffering from various diseases, found that there was a spontaneous precipitation of protein in 31 cases when the serum was cooled to 4 C.[6] They proposed the term cryoglobulin to describe the protein or group of proteins which have the characteristic of precipitation, or "gelifying," in the cold. The precipitated protein, which they regarded as a nonspecific indication of a disease state, would redissolve when warmed to 37 C. Lerner and Watson found cryoglobulins in a man who developed purpuric lesions of his extremities on exposure to cold, and they suggested that the cryoglobulins precipitated in the capillaries of those areas where the temperature fell significantly below 37 C.

Cryoglobulinemia is not a rare condition, and it has been found chiefly in the following variety of clinical conditions with involvement of the reticuloendothelial system: multiple myeloma, chronic lymphatic leukemia, kala azar, malaria, rheumatoid arthritis, and subacute bacterial endocarditis.[1,7-15,35-41] When large amounts are found, multiple myeloma is frequently the cause. Cryoglobulinemia has also been reported in cirrhosis of the liver, hepatitis, pneumonia, tuberculosis, lymphosarcoma, bronchiectasis, asthma, coronary artery disease, rheumatic heart disease, chronic glomerulonephritis, polycythemia rubra vera, polyarteritis nodosa, disseminated lupus erythematosus, thromboembolic pulmonary vascular sclerosis, gout, brucellosis, and gangrene of the extremities.[1,14-21,26,32,42-44] There have also been four cases of cryoglobulinemia reported in which no underlying disease entity was found. "Essential cryoglobulinemia" has been used to describe these obscure cases.[1,23,33-35]

Small amounts of cryoglobulins (less than 25 mg. per 100 cc.) are frequently found, while large concentrations are not common. It is believed that only when present in higher concentrations are they considered responsible for clinical manifestations. However, the cryoglobulin level may be highly variable (from trace amounts up to 10 gm. per 100 cc.) in one person over the course of the illness, and no regular correlation or relationship has been found between the quantity present and the presence or severity of symptoms ascribed to cryoglobulins.[50]

It is suggested that cryoglobulins, because of their unusual solubility properties, cause stasis and sludging of blood.[1,6,22,33] This may be transient or reversible, as in Ray-

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naud's phenomenon, or may continue and cause tissue anoxia, which, in turn, causes more sludging, resulting in the formation of thrombi.[31] This theory is favored by the postmortem demonstration of intravascular gelatinous material resembling precipitated protein in the heart and great vessels, cerebral vessels, pulmonary arterioles, small visceral vessels, and vessels in the extremities.[1,15,19,24,25,27,34,46-48] Some investigators believe that there probably is a complex mechanism which includes infiltration of the vessel wall by cryoglobulin and its interference with the formation of thromboplastin and fibrin.[31] Besides simple precipitation, which is influenced by the concentration of cryoglobulins, the blood viscosity and temperature, Volpé, Bruce-Robertson, Fletcher, and Charles suggest a sensitivity to the precipitated cryoglobulins. The latter may thus act like a foreign protein and cause local and systemic reactions.[45] This theory assumes a sensitivity to the precipitated protein which is absent when it is in solution. These authors obtained favorable results by treatment with corticotropin (ACTH) without accompanying significant decrease in the cryoglobulin concentration and offer this as supportive evidence of the "sensitivity" theory.

The cryoglobulins, which are thought to be part of the γ-globulin fraction, have a relatively high molecular weight, of 190,000 to 200,000. However, the molecular weight may vary to over 1,000,000.[50] These proteins are probably produced by the reticuloendothelial-plasmacyte system.[50]

Studies on cryoglobulins indicate that the degree of precipitation varies directly with their concentration and inversely with the temperature. Increasing the concentration of these proteins leads to an elevation of the temperature at which precipitation begins. In vitro studies have demonstrated their precipitation at temperatures occurring within the body.[45] Volpé, Bruce-Robertson, Fletcher, and Charles showed an increase in viscosity of serum containing cryoglobulins in comparison with normal serum. This was noted at body temperature and was more marked at lower temperatures.[45] The minimum concentration required for massive reversible precipitation has been thought to be about 1 gm. per 100 cc.[2,50]

The test for the presence of cryoglobulinemia is relatively simple. About 6 to 8 cc. of blood is withdrawn from the patient and kept warm. (In some cases with high concentrations of cryoglobulins, the syringe must be prewarmed to keep the cryoglobulins from precipitating). The blood is centrifuged for five minutes while warm, and then the specimen of serum is put in a refrigerator at 4 C for 24 to 48 hours. It is important that the blood specimen be kept warm prior to centrifugation; otherwise, the cryoglobulins may precipitate out with the cells. Cryoglobulins are considered to be present if the serum becomes cloudy owing to the protein precipitation in the specimen when exposed to the cold. (The serum or plasma may appear clotted in toto or may be divided into two layers: an upper layer containing normal plasma or serum, which may be faintly stained by bilirubin, and a lower layer, which is cloudy or whitish in color, owing to the precipitated cryoglobulin.) A positive test is confirmed if the cloudy serum then becomes clear when warmed to 37 C. Usually, in the first 24 to 48 hours the protein will precipitate, but 7 days has been set by some investigators as the time limit allowing any cryoglobulins to "gelify." The consistency of the cryoglobulins in serum samples refrigerated for one week or longer increases and a much firmer gel is formed than in fresh specimens.[45] Stefanini and Dameschek recommend incubation at 4 C (refrigerator) for only four hours in a screening test for the detection of cryoglobulins.[31] They also advise putting a second serum or plasma sample in incubation at 37 C (water bath) for the same time. If cryoglobulins are present, no changes should be observed in the sample kept at 37 C. The concentration of cryoglobulins in serum is usually estimated from the difference in serum total

protein before and after cold precipitation. However, many laboratories simply report the test as positive or negative, since no correlation has been found between the quantity present and the symptomatology ascribed to the cryoglobulins.

There is a lack of uniform characteristics attributable to cryoglobulins.[50] Systemic clinical manifestations thought to be directly due to these cold-precipitable serum proteins (those which precipitate in the cold) include cold sensitivity, Raynaud's phenomenon, epistaxis, stomatitis, deafness, retinal vascular stasis and hemorrhages, purpura, gangrene, blotchy pigmentation, venous thromboses, pulmonary infarcts, melena, abdominal distress, diarrhea, cerebral purpura, dyspnea, rigors, fever, and cyanosis.[45,50]

Many reports in the literature of cryoglobulinemia, which include eye findings, describe dilated retinal veins, retinal hemorrhages, and exudates.[1,2,4,7,9,28-30] In a case reported by Barr, Reader, and Wheeler, in 1950, Dr. John McLean examined the conjunctival vessels with a slit lamp and noticed aggregations of red blood cells and a generally slow circulation.[1] Application of ice to the conjunctiva reduced the circulation excessively, with segmentation of blood columns and even reversal of blood flow in some cases. The ophthalmoscopic findings sometimes suggested thrombosis in smaller retinal vessels, and there are several reports of thrombosis of the central retinal vein.[1,3,4,22,24,25,27,28] Anderson and Samuelson believed there were multiple emboli and thrombi in vessels of both eye grounds of a patient.[3] They described a cherry red spot in the fovea centralis and resultant vision of light perception in one eye and counting fingers in the other eye. So their case may have been one of central retinal artery occlusion. Other eye findings reported with cryoglobulinemia include narrowing and tortuosity of retinal arterioles, "silver wire" arteries, partial occlusion of blood flow, preretinal and vitreous hemorrhages, neovascularization, retinitis proliferans, grayish discoloration of the eyegrounds, macular degenerative changes surrounded by tiny hemorrhages, irregularity of venous caliber with localized constrictions not occurring at the arteriole venous crossings, and hemorrhages or telangiectasis on the iris surface.[1,3,7,9,24,27-29]

Berneaud-Kötz and Jahnke, in 1954, proposed the name "fundus paraproteinaemicus" to describe the retinal lesions caused by serum protein changes. They reported a case of hyperproteinemia, hyperglobulinemia, and cryoglobulinemia in which the fundus showed engorged cyanotic retinal veins with sausage-like constrictions, narrow arteries, many retinal hemorrhages, and edema of the discs and of the peripapillary and macular portions of the retina.[5] Danis, Brauman and Coppez, in 1955, reported two cases of multiple myeloma with cryoglobulinemia.[28] They believe that the fundus picture in myeloma with cryoglobulinemia resembles thrombosis of the central retinal vein and the fundus seen in blood diseases such as polycythemia and leukemia. In these conditions, the increase in blood viscosity is due to an increase in the formed elements of the blood rather than to cryoglobulins.

The usual treatment of cryoglobulinemia has been directed to the underlying disease. Israels and Kilgore used radioactive phosphorus (P^{32}) in a case of polycythemia rubra vera, and this treatment caused the cryoglobulinemia to disappear.[42] Osserman and Hines used 6-mercaptopurine to cause a temporary disappearance of the cryoglobulins in a case of multiple myeloma with cryoglobulinemia.[40] There are many reports of the use of corticotropin and cortisone, but it is much too early to evaluate this therapy.[23,33,37,39,43,45]

Report of a Case

A 33-year-old Negro man was first admitted to the Veterans Administration Hospital, Philadelphia, on March 3, 1954, because of orthopnea, dyspnea, and ankle edema.

His past history revealed that a positive serological test for syphilis, first noted in June, 1943, persisted despite several courses of treatment with penicillin and heavy metals.

He was treated for rheumatic fever while in the Army at Fort Dix in 1945, for five months, and again for a recurrence two years later.

In 1946 he noted sensitivity of the hands to cold and he first developed ulcers of his finger tips at that time. It was believed that he had Raynaud's disease. In 1947 a bilateral cervical sympathectomy was performed, but it resulted in only temporary relief. At this time, mitral and systolic and diastolic murmurs were noted as well as hypertension.

Recurrent episodes of fever, dyspnea, and polyarthritis continued between 1947 and 1950, necessitating a salt-restricted diet and digitalis. In 1953 skin and muscle biopsies were reported as normal. Digitalis was discontinued six months prior to admission, but the patient gradually developed cardiac decompensation.

On admission the physical examination revealed that the patient was in acute cardiac congestive failure. Temperature was 98.0 F; pulse rate, 100 per minute; respirations, 26 per minute; blood pressure, 170/140. His neck veins were distended, and rales were heard over the lower half of each lung field. The heart was enlarged and had a systolic and diastolic murmur at the apex. The liver was enlarged and palpable 3 cm. below the right costal margin and was slightly tender. There was moderate edema of the feet and ankles. The skin of the fingers was shiny and atrophic, and flexion deformities were present in all the fingers. Several finger tips of each hand were ulcerated. It was believed that the patient had generalized scleroderma.

Eye examination revealed 6/5 uncorrected visual acuity in each eye. External and slit lamp examinations were normal, except for a chalazion of the right upper lid. The intraocular tension was 20 mm. of mercury (Schiøtz) in each eye. Ophthalmoscopic examination disclosed Grade 2 hypertensive changes (moderate arteriole narrowing). There was sheathing of a segment of the superior temporal vein in the right eye and of the superior nasal vein in the left eye. There were several small red spots interpreted as deep hemorrhages or microaneurysms throughout each fundus.

Laboratory studies revealed a leukocyte count of 7900/cu. mm., with a normal differential count, a hemoglobin level of 12.5 gm., a hematocrit value of 40%, and a sedimentation rate of 33 mm. in an hour. The urinalysis was normal except for slight albuminuria. There was no Bence Jones protein in the urine, and hepatic and renal function tests were normal. Blood urea nitrogen, blood glucose, and serum chlorides, sodium, potassium, and CO_2-combining power were normal.

Cold agglutination test and bone marrow aspiration were negative. Generalized cardiac enlargement was noted on chest roentgenogram, and similar studies of the skeletal system disclosed beginning destruction and sharpening of the tufts of the terminal phalanges of all fingers, suggesting scleroderma. A gastrointestinal series was interpreted as showing hypoperistalsis of the esophagus consistent with the diagnosis of scleroderma. An intravenous urogram was normal.

The total protein varied between 9.4 and 10.0 gm/100 cc., with albumin of 3.5 to 3.7 gm. and globulin of 5.7 to 6.5 gm. When the serum was cooled to 4 C for 48 to 72 hours, a dense gel formed. Warming immediately dispersed the gel. The difference between serum protein determinations performed at 37 C and those determined after centrifugation and separation of the cold-precipitable proteins averaged about 1 gm. This was thought to represent the amount of cryoglobulins present.

It was thought that the patient had scleroderma, and he rapidly improved after treatment with digitalis, diuretics, and a low-salt diet.

His second admission to the hospital was on Oct. 17, 1954, because of the sudden onset of disorientation, maniacal behavior, and auditory and visual hallucinations. The physical and laboratory findings were essentially unchanged from those at the time of discharge from the hospital. Neurological examination was normal. An ocular examination on Nov. 2, 1954, was similar to his previous examination except for some changes in his fundus. The Grade 2 hypertensive changes persisted, but, in addition to this, a cytoid body or a cotton-wool patch was noted inferotemporal to the macula of the right eye. The superior temporal vein was sheathed as before, and now there were segments of other medium-sized veins which were sheathed, especially the superior nasal vein. Several microaneurysms were seen scattered throughout the posterior pole. In the left eye a cytoid body was noted below the disc and there were several microaneurysms in the posterior pole.

Although the cause of his abnormal behavior could not be found, the patient recovered with supportive therapy and sedation and was discharged on Nov. 5, 1954.

The patient was readmitted for the third time on March 24, 1955, because of sudden loss of vision in his right eye four days prior to admission. The visual acuity in the right eye was counting fingers, and acuity in the left eye was 6/6. External and slit lamp examinations were unchanged. However, ophthalmoscopic examination showed the picture of occlusion of the central retinal artery in the right eye. There was marked retinal edema surrounding the disc, macula, and posterior pole and a characteristic cherry red spot in the macula. The arterioles of the right eye showed generalized attenuation, which was more marked than in the left eye, and sludging of blood in the vessels. Ophthalmoscopic examination of the left eye revealed a Grade 2 hypertensive retinopathy and some neovascularization in the posterior pole. No hemorrhages were seen. The macula and periphery were normal.

Visual field examination, at this time, revealed a large central scotoma to a 20 mm. white test object. This central scotoma had extended 25 degrees nasally and to the blind spot temporally. The peripheral fields showed a slight generalized constriction, more marked inferiorly. Cryoglobulinemia was still present. The patient was placed on anticoagulant therapy.

On March 29, 1955, the central scotoma was much reduced in size, extending only about 15 degrees from the fixation point. There was much less edema present in the retina, and sludging of the blood in the veins was now evident only on digital pressure. On admission sludging had been present without digital pressure.

On April 3, 1955, the patient was readmitted because of pneumonia. At this time, the vision in the right eye had improved to 6/30 without correction. The central fields showed a 10-degree central scotoma to a 2 mm. white test object and only a small paracentral scotoma to a 5 mm. test object.

Ophthalmoscopic examination revealed pallor of the right disc and marked narrowing of the arterioles. The edema and cherry red spot had disappeared, and the retina showed a typical picture of an old central retinal artery occlusion.

The patient's fifth admission was on Aug. 25, 1955, because of gradual decrease in vision in the left eye for the previous three days. The visual acuity was still 6/30 in the right eye, but it was 6/7.5 in the left eye, where it previously was 6/6. The ophthalmoscopic examination of the right eye showed optic atrophy secondary to central artery occlusion, and the visual field was unchanged. The appearance of the fundus of the left eye suggested a partial central vein occlusion. There were many superficial hemorrhages, and there was engorgement of the veins. The arterioles were narrowed, and the macula exhibited many small round superficial hemorrhages. The visual field in the left eye showed a temporal paracentral scotoma extending 5 to 8 degrees from fixation.

General physcial examination revealed hypertension and the previously described changes of the digits. Cryoglobulins could not be found in the blood during this hospitalization. The patient was treated with anticoagulants, antibiotics, and prednisone. The hemorrhages absorbed within two weeks, and the visual acuity returned to 6/6.

The last admission to the Veterans Administration Hospital was on Dec. 31, 1955. The patient was rushed to the hospital in acute distress. He was aphasic and had left hemiparesis. The blood pressure was 220/150; pulse rate, 120 per minute; respirations, 40 per minute, and temperature 101 F. There was ptosis of the left lid. The pupils were miotic but reacted. The left eye was deviated to the left. There were numerous coarse rhonchi throughout the chest. The other positive findings were left 12th nerve paralysis and left hemiparesis. No abnormal reflexes were present. No further eye examination was performed.

It was believed that the patient had a right cerebral hemorrhage manifested by aphasia and left hemiparesis. Despite treatment with oxygen and crystalline procaine penicillin G (Crysticillin), the patient continued to go downhill rapidly and became less responsive and more comatose until 10:35 a. m., on Jan. 1, 1956, when he died.

Comment

In the case reported, the underlying vascular defect was most likely due to scleroderma. Involvement with this disease was evident in the hands, heart, and gastrointestinal tract. Although a definite relationship between the occurrence of cryoglobulinemia and occlusive vascular disease cannot be established, the cryoglobulins may have possibly contributed to the cold sensitivity, digital gangrene, and retinal artery occlusion and even to the brief psychotic episode.[25] Two other cases of cryoglobulinemia associated with hyperglobulinemia, cold sensitivity including involvement of the upper extremities, and gangrene of the digits have been seen at the Veterans Administration Hospital in Philadelphia.[32] These cases had no abnormal eye findings, but they did have occlusive arteriosclerotic disease, complicated by the presence of rheumatic heart disease in one.

Scleroderma is occasionally associated with disturbances in globulin, but cryoglobulinemia has not been reported. The origin of the cryoglobulins as well as the cause of the hyperglobulinemia are obscure in the case reported. There was an increase in all globulin fractions, and there was no specific electrophoretic pattern noted. No studies were performed to determine the specific globulin fraction which contained the cold-precipitable proteins.

Frequently cryoglobulins are noted to start to precipitate just below 37 C, with the precipitate becoming grossly apparent at 34 C. This temperature is well above that often attained in the hands during cold weather, and so it seems reasonable to postulate that this precipitate could cause symptoms of Raynaud's disease. Why should precipitation of protein occur in areas of the body such as the retinal vessels, where the temperature is not materially effected by external environment temperatures? Increase in cryoglobulin concentration leading to progressively higher temperatures of precipitation and increased blood viscosity may possibly help to explain the answer. Possibly the cryoglobulins infiltrate the vessel walls or cause a sensitivity reaction when precipitated, which they do not cause when in solution.[31,45] However, whether or not precipitation of cryoglobulins commonly occurs in deep vessels is still uncertain.[50]

It seems possible that cryoglobulinemia may be one of several factors involved in the pathogenesis of retinal vessel occlusion. Only by future investigation for the presence of these cold-precipitable proteins will we learn what role they may play.

Summary

The nature of cryoglobulinemia is discussed, and one case of occlusion of the

central retinal artery associated with cryoglobulinemia is reported. The patient also had cold sensitivity and gangrene of the digits, probably due to scleroderma. It is possible that the cryoglobulins may have been a contributing factor in the central retinal artery occlusion. A search for the presence of these cold-precipitable proteins is indicated in all cases of obscure vascular occlusions.

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Ocular Myopathy Associated with Retinitis Pigmentosa

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Ocular myopathy is better known in the ophthalmic and neurologic literature as "chronic progressive nuclear ophthalmoplegia" or as "chronic progressive external ophthalmoplegia." The various terms stem from differences in opinion as to what constitutes the basic pathologic process. The older concept of nuclear origin in this entity [1,2] was that of a degeneration of the nuclei of the oculomotor, trochlear, and abducens nerves. However, more recent pathologic studies [3-6] indicate that this conclusion is not justified. Sorsby [7] is of the opinion that ocular myopathy bears no relationship to motor neuron disease but is a form of muscular dystrophy. The pathologic data accumulated to date indicate that "chronic progressive external ophthalmoplegia" may rightly be considered as an "ocular myopathy," which is well summarized by Kiloh and Nevin.[4]

While uncommon, cases of progressive muscular dystrophy are reported in which the ocular muscles and muscles of the eyelids have been involved.[8] Ocular myopathy may be a variant in the localization of a dystrophic process, since the lesions in the ocular muscles are comparable to those found systemically in progressive muscular dystrophy. Adler [9] has stated that, unless we are dealing with two separate disease entities with a different pathogenesis, one must assume that the cases of so-called chronic progressive ophthalmoplegia belong in the group of ocular myopathies and are due to some primary disturbance in the ocular muscles themselves.

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In the recent literature, there are several clinical case reports of ocular myopathy.[10-13]

The clinical picture of ocular myopathy consists of a slowly progressive weakness of the muscles of the eyelids and of the extraocular muscles without further evidence of central nervous system involvement. The orbicularis oculi, other facial muscles, and neck and shoulder muscles, at times, may be similarly involved. The onset is insidious from infancy or, usually, prior to the age of 30, gradually involving more and more muscles, until finally, after many years, severe ptosis and external ophthalmoplegia are present. Ptosis may be the first sign, or the onset of ptosis and external ophthalmoplegia may be simultaneous. The process may be bilateral or unilateral. When bilateral, asymmetry in degree of involvement may be present. The process may be arrested temporarily or permanently at any point, but remissions do not occur. The pupils remain unaffected. Diplopia is usually absent owing to the long insidious course of the disease, but a slight divergent strabismus is usually present when the ophthalmoplegia is advanced. There is no apparent sexual preponderance, but a familial incidence is common.

Schwarz and Liu [6] have reported one case with a complete neuropathologic evaluation of the nuclei of the third, fourth, and sixth cranial nerves and of the extraocular muscles. The motor nuclei and the nerve fibers to the extraocular muscles were reported as being normal. Histologic study of the extraocular muscles revealed atrophy, swelling, hyalinization, and fragmentation of the muscle fibers, with a loss of striations. Phagocytosis of disrupted myofibrils, overgrowth of fat, and connective tissue replacement of the destroyed muscle fibers were present. This muscle pathology is in

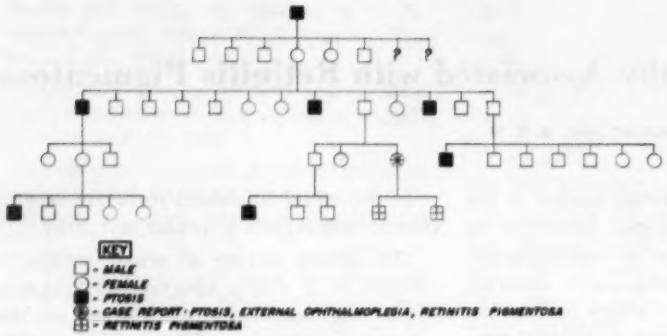

Fig. 1.—Family pedigree.

agreement with that found by others.[3-5] Recently, Kurus [14] has reported three cases of external ophthalmoplegia in which stellate ganglion block accentuated the ptosis, suggesting that neither the sympathetic nerves nor Müller's muscle are involved in the myopathy.

Rarely, retinal changes are associated with ocular myopathy. Barnard and Scholz [15] and Walsh [16] have each reported four cases of external ophthalmoplegia associated with retinitis pigmentosa, and they are of the opinion that this may well represent a syndrome rather than a fortuitous association. Three cases have also been reported by Chamlin,[17] who refers to them as a heredo- associated with retinitis pigmentosa has degenerative entity. Furthermore, the occurrence of progressive muscular dystrophy been reported.[18]

It has been pointed out by Sorsby [19] that within given families with external ophthalmoplegia a particular type of muscular defect tends to occur, such as an isolated ptosis, an abducens palsy, an isolated vertical muscle palsy, or a total or an incomplete external ophthalmoplegia. Yet, the possible unity of the different clinical types is suggested by the fact that in large families transitional forms occur. The occurrence of retinitis pigmentosa with external ophthalmoplegia may be a variant wherein the retinal changes act as an equivalent of the muscular disease.

The occurrence of ptosis, external ophthalmoplegia, and retinitis pigmentosa is illustrated in the family pedigree of the case here reported (Fig. 1). A ptosis present at birth is the marked feature in this pedigree (Fig. 2), and the condition has a recessive inheritance. Since the degree of involvement of the other extraocular muscles varies with different families, the case reported here may represent a sporadic extensive dystrophy of all the extraocular muscles. The association of retinitis pigmentosa here has an uncertain genetic status.

Fig. 2.—Paternal great grandfather of the patient, with ptosis on the left side.

Report of a Case

A 25-year-old housewife was first seen in November, 1955, with a complaint of difficulty in reading. Her past history revealed that she has had a bilateral ptosis since birth and that she has had difficulty seeing at night for as long as she can remember. At the age of 13, after an examination of her eyegrounds, she was told that she had "black spots" in her eyes. Since the age of 16 she has had difficulty in rotating her eyes and in looking to the side without turning her head.

The ocular examination showed the vision to be 20/30, corrected with a mixed astigmatic glass to 20/20 and J-1. The pupils were normal and dilated well with mydriatics. A moderate degree of bilateral ptosis was present, which was more marked on the left (Fig. 3). There was a marked limitation of ocular rotations, especially dextroversion, to about 10 to 15 degrees.

Fig. 3.—Patient, with bilateral ptosis.

Voluntary and following upward gaze and Bell's phenomenon were absent. In the primary position at near there was a small degree of exotropia, with a remote near point of convergence. Opticokinetic nystagmus could be elicited in both the horizontal and the vertical direction, but the excursions were slight. Ophthalmoscopy revealed a moderate peripapillary atrophy, a diffuse macular pigmentary disturbance with poor foveal reflexes, a definite attenuation of the retinal vessels, and, in the periphery, scattered clumps of pigment. These retinal changes were present bilaterally but were more marked in the left eye. The visual fields showed an irregular concentric contraction down to a radius of 30 to 35 degrees.

The general examination revealed only a thin woman with a wide spacing between the first two toes, and the neurological examination was within normal limits except for a bilateral orbicularis oculi weakness. The serology, skull x-rays, and a test for myasthenia gravis with intravenous administration of edrophonium (Tensilon) chloride were negative.

Ocular therapy consisted of a ptosis crutch and a glass for near with base-in prisms.

In February, 1956, the parents of the patient were examined, and they exhibited no ocular abnormalities. The patient's two sons, ages 2 and 3 years, were also examined, and both were found to have early ophthalmoscopic signs of retinitis pigmentosa but were without demonstrable extraocular muscle abnormalities. Clinical signs of an ocular myopathy in these offspring may develop subsequently.

Summary

Ocular myopathy is a clinical entity consisting of progressive hereditary ptosis and external ophthalmoplegia. It may be considered as a subgroup of progressive muscular dystrophy, as has been demonstrated by recent neuropathologic studies. The rare association of retinitis pigmentosa with

ocular myopathy is presented in a patient with a family pedigree of five generations exhibiting the occurrence of ptosis, external ophthalmoplegia, and retinal changes.

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Local Irritating Effect Caused by Topical Use of Steroids in the Eye

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About a half a decade has elapsed since the introduction of the therapeutic use of corticosteroids. Experience has been accumulated as to their effectiveness in various ophthalmic diseases by systemic as well as by topical administration (Gordon, 1955 [16]; Hogan, 1955 [8]; Steffenson, 1955 [9]). The splendid therapeutic responses have overshadowed the local irritating effects of such topical preparations. Reports of such undesirable local side-effects are very brief, rare, and contradictory.

Previous Reports

The following citations from the literature will illustrate this point.

A. Older Reports Dealing with Cortisone.—Woods, 1950 [1]: A 2.5% suspension without buffer "caused mild transient irritation which passed in a few minutes." Woods, 1951 [2]: "This suspension" (in buffered vehicle with added preservative) "is completely non-irritating, in fact is somewhat soothing to an inflamed eye." Duke-Elder, 1951 [3]: "This is completely non-irritating, even if the undiluted suspension is used." Leopold et al., 1951 [4]: "There was no undue reaction, nor subjective complaint following the use of diluted cortisone suspensions as drops." Fine and Goodwin, 1952 [5]: "Full strength cortisone produces only mild irritative symptoms. . . ." Steffenson et al., 1952 [6]: "Stronger solutions were mildly irritating, but it was not clear whether this was due to the cortisone itself or to the suspending agents and preservative." Lopez, 1954 [7]: "A minimum of discomfort was noted by most patients" (after use of neomycin-cortisone ointment).

B. Reports Dealing with Hydrocortisone.—Hogan et al., 1955,[8] did not mention any local irritating side-effects at all, although they surveyed their experience with almost 1000 topically treated cases. Steffenson, 1955 [9]: "In certain cases, prolonged use of local hydrocortisone causes stippling of the corneal epithelium which disappears immediately after the drug is discontinued. This mild irritative effect is apparently caused by the vehicle in which hydrocortisone is suspended."

C. Reports Dealing with Prednisone or Prednisolone.—King and Weimer, 1955 [10]: "Local irritation due to the topical administration of these corticosteroid preparations was seldom noted on the two hour administration schedule. If the time was increased to every hour, the ointment became more irritating. . . . The suspensions were momentarily irritating." Hogan et al., 1955 [11]: "A moderate number of patients complained of stinging and burning when the drops are used, but this was believed to be due to the vehicle employed." King et al., 1955 [12]: "The alcohol forms are slightly more irritating than the acetate."

Abrahamson and Abrahamson, 1956,[13] reviewed 350 cases in which Metimyd (a suspension of prednisolone acetate and sulfacetamide sodium [sodium Sulamyd] and neomycin) was used. "No ill effects other than a slight burning sensation lasting seconds were encountered." Gordon, 1956,[14] in a report on 179 patients, does not mention any local side-action. "It must be emphasized that no contraindication exists

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to continuous topical therapy with prednisone or prednisolone." O'Rourke et al., 1956,[15] do not discuss local side-effects in their small number of human cases.

D. Reports Dealing with Fludrocortisone.—Gordon, 1955,[16] does not mention which form of this steroid he used. He states: "Since it is in solution [!], it is less irritating." However, Steffenson, 1955,[9] reporting on the acetate form, states, "The 9-alpha-fluorohydrocortisone acetate suspensions [!] and ointments elicit more subjective responses of irritation."

E. Dermatologic Reports.—For the sake of comparison, reports in the dermatologic literature ought to be mentioned describing "some occurrence of local irritations from the preparations" (ointments and lotions of prednisone and prednisolone) (Hollander, 1955[17]).

Present Report

It is the purpose of this report to draw attention to local irritating side-effects caused by topical use of corticosteroids in the eye. This report is not intended to advocate discontinuance of these proved therapeutic aids. However, in view of their widespread use, any side-effects ought to be common knowledge.

More patients notice local irritating effects in the eye caused by topical use of steroids than one would expect after surveying the existing literature. In such patients, I frequently observed deposits of whitish crystals in the conjunctival sac, on the caruncle, or on the lid margins after topical use of steroid preparations. I attributed the uncomfortable effect to the mechanical irritation caused by these white particles. Examples of such patients represent a cross section of cases in which the use of steroids is indicated (e. g., postoperative iritis, nongranulomatous iritis, superficial keratitis, episcleritis, etc.). Preparations causing such irritating deposits in this study comprise a variety of products by different manufacturers: hydrocortisone (Hydrocortone) acetate ophthalmic suspension, 2.5%, Sharp & Dohme; Neo-Cortef ophthalmic suspension, Upjohn (containing 1.5% hydrocortisone acetate and neomycin sulfate); Cortisporin ophthalmic ointment, Burroughs Welcome & Company (containing hydrocortisone 1% and a mixture of antibiotics); Terracortril ophthalmic suspension, Pfizer (containing 1.5% hydrocortisone and oxytetracycline [Terramycin]); tetracycline (Achromycin) with hydrocortisone (1.5%) ophthalmic ointment, Lederle; and Metimyd ophthalmic suspension, Schering (containing prednisolone acetate 0.5%, sulfacetamide sodium, and neomycin sulfate).

Objective proof of the presence of such irritating deposits in the eyes was obtained by several photographs. Not infrequently one sees the crystalline steroid deposits intimately mixed with mucous conjunctival discharge, forming white strands. Figure 1 illustrates such a case.

To exclude any doubts as to the chemical nature of these white irritating deposits on the eyes, scrapings of the material were obtained. The deposits were proved by chromatography (qualitative analysis) to be steroids. It is interesting to note that these crystals on the conjunctival fornix or the caruncle or lids remain there for a long time after the administration of the steroid. The specimen analyzed in this study was obtained from the eye eight hours after instillation of Neo-Cortef suspension (Upjohn).

As an example of the subjective complaints of patients, I quote the following description by a careful observer (university instructor of clinical psychology). He used Cortisporin ointment for bilateral superficial punctate keratitis and stated: "A scratchy sensation (like glass in the eye) occurs after each use of the ointment. The sensation lasts about two hours and relief occurs after mild whitish discharge is extruded at the inner lid angle."

The exact incidence of such formation of steroid deposits in patients receiving topical

Fig. 1.—Treatment of superficial keratitis. Deposits of steroids photographed two and one-half hours after instillation of hydrocortisone acetate and neomycin sulfate (Neo-Cortef) ophthalmic suspension.

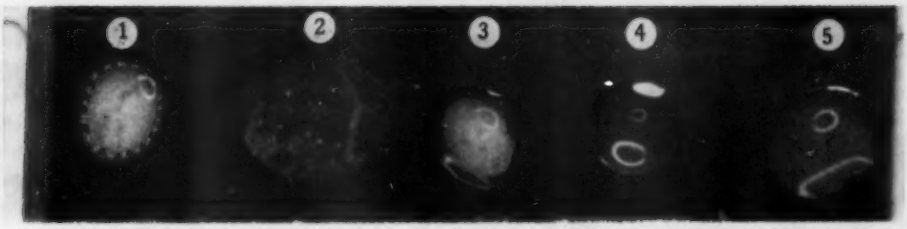

Fig. 2.—Glass slide bearing drops or smear of five different available steroid ophthalmic medications. Steroid particles can be seen with the naked eye. (1) Hydrocortisone acetate 0.5% suspension, Sharp & Dohme. (2) Tetracycline with hydrocortisone 1.5% ointment, Lederle (smear). (3) Prednisolone acetate 0.5% with sulfacetamide, Schering. (4) Prednisolone phosphate (with neomycin) suspension, Sharp & Dohme, experimental. (5) Fludrocortisone acetate 0.1% suspension (with neomycin and gramicidin), Squibb.

treatment was not determined, since this study deals with ambulatory patients seen in private practice. In comparison, steroid suspensions are more frequent offenders than the steroid ointments (disregarding the annoyance caused by any ointment base itself). The appearance of steroid deposits around the eye was frequent, yet not absolutely regular. Some patients were observed on different occasions, showing the deposits after each use of the medication. The irregularity may be related to the particular batch of the steroid preparations used by those patients.

It is not surprising to encounter such deposits in the eye. When one looks at the bottles containing steroid suspensions, the steroid crystals can easily be seen settled at the bottom, and it is obvious that insufficient and irregular distribution of particles will occur after inadequate shaking. The clumpy accumulation is likely to be mechanically irritating. Particles contained in the ophthalmic ointments are not so often discovered, because they are kept in nontransparent tubes, but one can find them by making a smear on a glass slide. Figure 2 shows such a smear and drops of various suspensions.

Pharmaceutical researchers have been concerned with the problem of the particle size of steroids. Pifer, 1955,[18] states: "We are aware of this handicap" (i. e., mechanical irritation of the eye by the steroid preparation). At his laboratory, they "micronized the crystals to a very small particle size." Smith, 1955,[19] also states: "We had given some thought to particle size." The pharmaceutical industry is endeavoring to produce ophthalmic steroid preparations containing the finest possible particle sizes. However, all commercially available eye drops are suspensions, not solutions; ointments do not do much better in distributing the steroid particles evenly. The newest available steroids, prednisone and prednisolone, share this disadvantage with the older preparations, and so do the available

TABLE 1.—*Comparative Measurement of the Particle Sizes of Ophthalmic Steroid Preparations*

Drug	Particle Size	Comment
Hydrocortisone acetate suspension 2.5%, Sharpe & Dohme	2μ	Stable in individual size, but frequent clumping up to 30μ in size
Prednisolone acetate 0.5% suspension and sodium sulfacetamide, Schering	3μ-6μ (many crystalline ones, 1μ-2μ)	Enormous variation in size; enormous clumping
Prednisolone acetate 0.5% suspension with sulfacetamide and neomycin, Schering*	Same as the same product without neomycin	More clumping than the same product without neomycin
Fludrocortisone acetate 0.1% suspension with neomycin and gramicidin, Squibb	4μ-13μ	Many crystalline particles; moderate clumping
Hydrocortisone acetate 1.5% with tetracycline ointment, Lederle	5μ-8μ (some up to 30μ)	Variable size; many crystalline particles

* This preparation was supplied by Dr. Harry V. Pifer, Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

fludrocortisone preparations. King and Weimer, 1955,[10] also mention in their extensive study on prednisone that it "requires much agitation to form an even suspension."

My own study of various commercially available preparations has shown that there is considerable variation of the individual particle size in the same bottle as well as variability between different bottles. The greatest difference in appearance is caused by clumping; the size of the individual particles counts less than their tendency to form larger clumps. The clumping is dependent on various factors, such as temperature changes, standing, age of the bottle, etc. Thus, the production of very fine particles does not necessarily prevent uneven distribution. Table 1 shows the particle sizes of several available steroid preparations.

Comparative measurements in pharmaceutical laboratories show these results; for prednisone alcohol, 2μ-45μ; for prednisolone acetate, 25μ. Variable size was also noted (Pifer, 1956[20]). All available preparations contain steroids either in their acetate form or as free alcohol. Most products are marketed in the acetate form mainly because of its greater stability and longer shelf-life.

Pharmaceutical research, at present, is directed toward producing other steroid compounds which may be more or less true solutions in the physicochemical sense. I had the opportunity of examining one of those experimental preparations, prednisolone phosphate.

The qualities of prednisolone phosphate appear to be more desirable in this respect than those of all previous preparations. The phosphate appears grossly as almost a true solution. In the small number of patients treated with it, the phosphate form has prevented the local irritating effect caused by the large clumping particles, has been more acceptable to the patients, and has been clinically effective. Results of examination of this product are shown in Table 2.

Table 2 shows that these preparations do contain larger particles. They are not true solutions in the physicochemical sense. However, the absence of clumping provides the characteristics of a clear solution in the pharmaceutical sense. The glass slide in Figure 2 (Specimen 4) illustrates this property.

At the present state of our knowledge, encouragement ought to be given to any efforts to produce truly soluble ophthalmic steroid preparations, which avoid the local side-effects described in this paper. However, further research will be necessary in order to avoid other disadvantages which may possibly accompany the use of true solutions. Gordon[16] has suggested that better solubility apparently means better tissue penetration but more transient action. It has been shown by many investigators (Hogan,[11] Leopold,[21] and others) that tissue penetration and clinical effectiveness of topical steroid preparations are not necessarily parallel. Steroids which penetrate better or faster into the globe show less surface effectiveness. In certain clinical uses higher esters of hydrocortisone are preferred because of their slow tissue penetration and absorption, e. g., in intra-articular injections. Similarly, ophthalmic preparations showing slower absorption may be

TABLE 2.—*Particle Size of Prednisolone Phosphate*

Drug*	Particle Size	Comment
Prednisolone phosphate, plain	Most are less than 5μ, but occasionally up to 50μ	Many globular particles; some crystalline particles 20μ long; no clumping except small groups, the individual particles of which are 0.5μ to 1.5μ.
Prednisolone phosphate, with neomycin	Same as the same product without neomycin	Some polymorphous particles; no crystalline particles; no clumping

* These preparations were supplied by Dr. R. T. Smith, Assistant Director of Clinical Investigation, Sharpe & Dohme, Division of Merck & Co., Inc., West Point, Pa.

more desirable for surface lesions. Further research must show the possibilities of reaching deeper intraocular lesions by topical true solutions in which systemic steroids are now employed. It is conceivable that, in the future, two kinds of ophthalmic topical steroid preparations, with different indications, will be in use: one, more slowly absorbable and less soluble, for its antiphlogistic effect on the surface; another, more penetrating and more soluble, for its effect on more posterior segments of the eye.

Summary

References in the literature to local irritating effects caused by topical use of steroids in the eye are reviewed. Attention is drawn to the existence of such local side-effects. The side-effects are attributed to mechanical irritation by steroid particles contained in ophthalmic drugs and steroid deposits retained in the eyes. Photographic evidence and chemical proof of the existence of such steroid deposits is furnished. Various ophthalmic steroid preparations have been examined to determine the distribution and size of their steroid particles. True solutions (not suspensions) of steroids would be an advance of ophthalmic therapy because of elimination of irritating side-effects. The need for further research as to the potential use of true solutions of steroids in topical therapy of diseases of the posterior segment of the eye is indicated.

Dr. Elwood LaBrosse, Biochemistry Institute, University of Texas, gave help in the chemical analysis and measurement of particles.

The cost of the colored illustration was defrayed by a grant from Sharp & Dohme, Division of Merck & Co., Inc.

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The Position of the Eyes During Prism Vergence

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Introduction

If the positions of the eyes are recorded photographically [1-5] or observed with a telescope [6, 7] during the process of making a horizontal vergence movement, it can be demonstrated that the record of the relative position of the lines of sight of the two eyes may differ from the convergence angles of the test targets during single binocular fixation. The exact amount of this disparity differs according to the subject and the test conditions, but there is fairly good agreement that the order of magnitude is several degrees, i. e., much larger than the size usually postulated for Panum's fusional areas.[8] On the basis of such evidence, Tani, Ogle, Weaver, and Martens [5] have questioned the validity of optical measurements of eye movements by photographic or telescopic observation of details on the eyes themselves or of images from light reflected from the corneas. These authors believe the measurements to be in error because they do not believe that the lines of sight of the eyes can depart to this extent from the convergence angles involved during single binocular vision.

The question of the validity of these measurements is of extreme importance, since measurements of this sort form the principal basis of our understanding of eye movements. Such work began with the pioneering work of Dodge [9-11] and Judd [12] more than 50 years ago and extends down to our own time.[13]

Tani, Ogle, Weaver, and Martens suggest that the discrepancies result from shifts of the whole eye in the orbit (anterior-posterior and/or nasal-temporal) during the process of the vergence movements. Such ocular position shifts, if they occur, would so effect the record in an optical recorder of the eye movement that the position indicated for the lines of sight on the record would be erroneous. This speculation can be tested by studying the position of the eyes during a vergence movement with the use of a nonoptical measure of eye position. In some of the experiments to be reported here, the ocular rotational potential * (ORP) has been used to study the position of the eyes. Details of this technique have been described elsewhere.[14]

It should be emphasized that the shifts postulated by Tani, Ogle, Weaver, and Martens are only of the order of 0.1 mm. and are consequently difficult to measure directly. The rationale of the present experiment is that such small shifts would probably have a quite different effect upon the electrical record of eye position that is here employed than they would have upon an optical recording. Consequently, if the above speculations are correct, the present experiments should yield results which differ widely from those previously obtained by photography of eye position.

Experiment I

A. Method.—Measurements were made under conditions of "jump" vergence; that is, the response of the two eyes was measured after the sudden introduction of a prism, base-in or base-out, before one of the two eyes. Selection of these conditions should not result in ocular position shifts, if Tani, Ogle, Weaver, and Martens are

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* Term suggested by Dr. H. Richard Blackwell, who assisted in this work.

correct in their assumption that the ocular shifts occur only after the vergence movement has been prolonged for some time.

The subject was seated comfortably in a well-lighted but electrically shielded room and fixated binocularly a thin black vertical cord against a white background (3.2 foot-lamberts) in a 6-degree field. The distance of the cord from the spectacle plane was 25 cm. Grass skin electrodes were placed on the external and internal canthus of each eye; the ORP was amplified by an Offner direct-current amplifier and recorded by ink-writing pens on moving paper. The responses of each eye were recorded in a separate channel, and leads from the superior and inferior margins of the orbits were grounded to minimize electrical cross talk.

The procedure was to introduce suddenly a small amount of horizontal prism in the spectacle plane of the right eye while instructing the subject to keep the vertical cord unified. After the prism was before the eye for several seconds it was removed and the responses of the two eyes were again recorded. The process was repeated several times, with frequent rest periods between measurements, using prisms of varied power placed alternately base-in and base-out before the right eye.

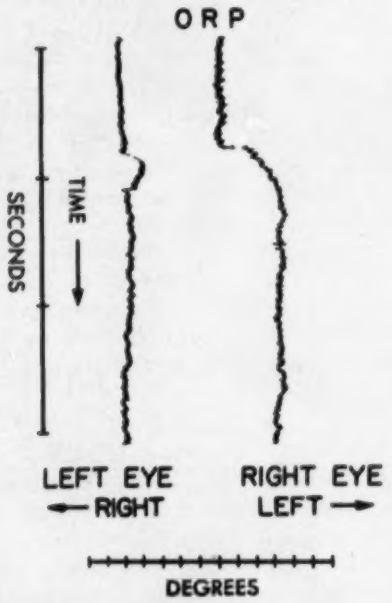

Fig. 1.—Ocular rotational potential response of the two eyes to the sudden introduction of 10△, base-out, before the right eye. Both eyes move to the left, but the left eye response returns to the original value. The test target was a black line on a white (3.2 foot-lambert) background at 25 cm. from the spectacle plane viewed in symmetrical convergence. (Subject S. S.)

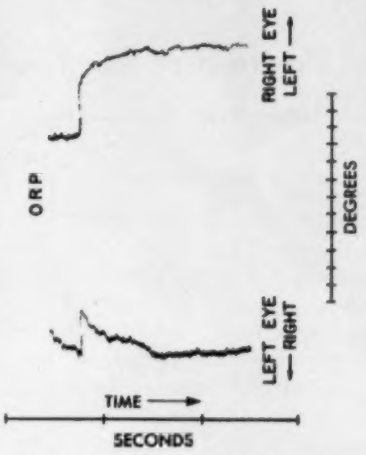

Fig. 2.—Ocular rotational potential response of the two eyes to the sudden removal of a 15△, base-in, from before the right eye. (Testing conditions otherwise the same as in experiment illustrated in Figure 1.)

To convert voltage differences into degrees of movement, the records were calibrated by obtaining a curve showing the voltage generated for various amounts of known, controlled (saccadic) eye movements. The relationship between amount of eye movement and voltage amplitude proved to be linear within the range of eye movements (less than 20 degrees) studied.

B. Results.—Typical responses of the eyes in this experiment are illustrated in Figure 1 and Figure 2.

Several important features of these responses, other than the precision of the measurement, should be emphasized. In the first place, it was invariably found by me that, contrary to the principle of least muscular effort described by Wundt [15] and contrary to the common description of this

phenomenon by Bielschowsky[16] that has repeatedly been emphasized in the textbooks,[17] both eyes move. The magnitude of the response of the eye which did not look through the prism was always smaller than that of the other eye, and it invariably returned to the position it had maintained prior to the change in vergence stimulus. The responses of the two eyes can be analyzed into a fast and a slow component. In the Figures presented, the movements were restricted to a single fast and a single slow component, but this was not always the case; a single movement on occasion had two or three fast components, each separated from the others by a slow movement. The fast components occurred simultaneously in the two eyes and were always in the same direction, indicating saccadic movements, the amplitudes of which were not always the same for the two eyes. On the other hand, the slow components of the movement for the two eyes were always in opposite directions, indicating a vergence movement, and the amplitudes of these movements were approximately the same for the two eyes. These findings have important implications for the theory of equal innervation for the muscles of the two eyes and will be discussed in some detail elsewhere.[18]

The principal results of the experiment are illustrated in Figure 3. Since the amplitude of the movement of the eye not looking through the prism was such that it always returned to its initial position, what is plotted on the ordinates in this Figure is the total amplitude of the movement of the right eye (i. e., the eye viewing through the prism). The abscissas are the magnitudes of the change in the stimulus to convergence in degrees.† The plotted points are the

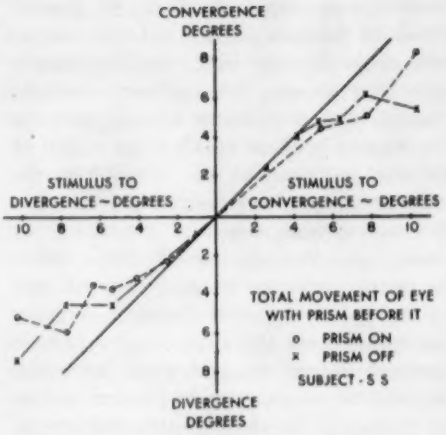

Fig. 3.—Summary of data showing the ocular rotational potential record of the response to prism base-in and base-out before the right eye of observer S. S. Ordinates are the electrical record of changes in convergence and divergence, while the absicissas are the changes in the stimulus to convergence and divergence. The origin of coordinates represents convergence on a vertical black line 25 cm. from the spectacle plane, and all other convergence and divergence values are relative to this zero position.

means of six measurements. If the movement of the eyes followed the stimulus perfectly, then the data should all fall on the straight line of unit slope.

These data show clearly, for jump vergence of any appreciable magnitude, that a disparity exists between the amplitude of the movement and the convergence angle of the targets. The magnitude of this discrepancy is of the order of several degrees, much larger than the size usually postulated for Panum's areas. It should be pointed out that the movement is invariably less than the stimulus and that the magnitude of the disparity tends to increase as the stimulus increases. This result is strikingly similar to Stewart's results[3, 4] with jump vergence when a photographic measurement of eye

† It is necessary to take account of the fact that the prism of rated power (α) is introduced in front of the spectacle plane, but that any motion of the eyes occurs at a distance 27 mm. behind the spectacle plane around a hypothetical "center of rotation." The correction for the "effective" power (β) of the prism is made by means of the following equation:

$$\beta=\left(\frac{t}{(1-0.027D)(t+s)+0.027}\right)\alpha$$

In this equation all distances are expressed in meters; t is the distance from the object viewed to the spectacle plane; s is the distance from the plane of the prism to the plane of the spectacle, and D is the spectacle correction, in diopters.

position was employed. Both the general trends of the data and the order of magnitude of the disparity in the two experiments agree very closely. This similarity in results suggests that it is highly unlikely that the discrepancy between the electrical record of the eye position and the stimulus to the movement can be exclusively attributed to the hypothetical construct postulated by Tani, Ogle, Weaver, and Martens. While an anterior-posterior or nasal-temporal shift of the eye in the orbit during a vergence movement (over and above what may have occurred during the calibration horizontal saccadic movements) might possibly lead to an artifact in the electrical measurement of eye position, it is unlikely that the order of magnitude and the direction of the artifact would be so similar with optical and electrical recording of eye position.

C. Comment.—In view of these results, it would seem necessary to entertain the possibility, at least, that during the process of the vergence movement the lines of sight of the two eyes do not intersect on the target. Tani, Ogle, Weaver, and Martens refuse to accept this possibility because "it must be assumed that for the maintenance of fusion the images of the fixated object received by the two eyes fall on the corresponding foveas of the retinas at least within the small angle of fixation disparity."[5] While these authors admit that methods of measurement of fixation disparity obtained with peripheral stimuli to fusional movements cannot be extrapolated for the center of the visual field, they believe that the theory of retinal correspondence would not permit fusion of objects in the center of the field with a disparity larger than the few minutes of arc suggested by peripheral fixation disparity experiments. Since they are unwilling to abandon the theory of retinal correspondence, they postulate the shifts of the eyes in their orbits to account for the experimental data.

It seems unnecessary to go to either of these extremes. More than 20 years ago Verhoeff[19] suggested that the process of unification should not be considered as an additive effect of the retinas of the two eyes to the perceived image. On the contrary, he regarded the whole process as one of reciprocal replacement. If the images became disparate, then he referred to the process as "quasi unification" and the disappearance of one of the images occurred by total replacement. It seems quite reasonable that some such process may be going on when a fusional movement is induced by suddenly placing a prism before one eye and the amplitude of the eye movement is less than the stimulus.

These concepts are of some value in that they predict the outcome of a workable experiment: If one views an undifferentiated purple field, it is possible to perceive entoptically what has been called Maxwell's spot. This perception, which has been variously attributed to the absorption of macular pigment,[20] to the concentric zonation of chromatic and intensity differences in terminal light produced by the changing profile of the foveal pit,[21] and to the distribution pattern of retinal color receptors in the fovea,[22] is universally agreed to be an entoptic image of the area centralis. If a normal observer fixates binocularly a vertical line on such a background, he perceives the Maxwell spot centered on the line. If now a prism is introduced suddenly before one eye, the concept of reciprocal replacement, when considered in light of the results shown in Figure 3, leads to the following alternate predictions:

(*a*) Upon binocular unification through the prism, Maxwell's spot will be still seen centered, but if one of the two eyes is suddenly covered the Maxwell spot should be seen immediately eccentric with respect to the line and only gradually return to a centered position. If the opposite eye were screened following unification, however, the spot should remain centered. This is explained by a replacement of the disparate image of the vertical line, as well as the replacement of the Maxwell spot of the same eye, during unification.

(*b*) The Maxwell spot will be seen eccentric during binocular fixation, the disparate Maxwell spot replacing the one in the centered eye.

The following experiment was set up to test the accuracy of the prediction of the above speculations.

Experiment II

A. Method.—A 300 watt projection bulb was mounted in an Argus 35 mm. projector placed inside and at one end of a black well-ventilated box approximately 1 meter long. The front end of the projector was approximately 55 cm. from the other end of the box, which was replaced by an opal glass approximately 32 cm. square. The lid of the box was closed to prevent any stray light from passing into the room. The light beam passed through a Wratten No. 2389 filter ‡ and thus produced a dichroic purple background through the opal glass which was approximately 28 cm. in diameter and had a luminance of about 5 foot-lamberts, as measured with a Macbeth illuminometer. A vertical plumb line of surgical thread was suspended immediately in front of the opal glass. The observer viewed this (15.6 degrees circular) field at 1 meter distance. With the room lights on, the Maxwell spot was invisible, but when all other illumination in the room was reduced the purple background demonstrated a clear Maxwell spot.

B. Results.—Young adults with normal binocular vision served as subjects. Each observer first utilized binocular fixation of the plumb line and demonstrated that Maxwell's spot was seen centered binocularly with either eye fixating. The subject was instructed to fixate the line continuously and to unify it at all times. With the room lights on, a prism, base-in (or out), was placed before the right eye. When the subject reported the plumb line unified, the room light was turned off and the position of Maxwell's spot was reported. The subjects usually responded according to prediction (*a*) above: i. e., the binocularly fixed Maxwell's spot was centered, but if one eye (usually, but not always, the eye not viewing through the prism) was suddenly occluded, Maxwell's spot momentarily appeared eccentric. This eccentricity would be maintained for several seconds after the eye was screened but would gradually return to "fixation line." By quickly moving a second target (thread or a pencil point) into the field, it was possible to get an estimation of the amount of eccentricity of the spot at the moment when the eye was screened. Frequent turning on and off of the room lights was required, because the spot tends to disappear after continuous exposure for several seconds. From the magnitude of the eccentricity measured it was possible to calculate an estimate of the angular separation of the lines of sight at the moment when the eye was screened. This estimate, though, approximate, would tend to err in the direction of giving a smaller measure of eccentricity, since the spot tended to move toward the fixation line as soon as the eye was screened. It should be emphasized that the eccentricity obtained must have been produced by the fusional movement, since monocular fixation either with or without the prism produced no such eccentricity, nor did binocular viewing of the line without the prism. One subject reported as in prediction (*b*), but detailed measurements were not made for this observer. All others reported as in prediction (*a*).

The results of this experiment for two observers are illustrated in Figure 4. Each point is the mean of five measurements. The ordinates are the calculated changes in the angles of convergence in degrees, while the abscissas are the changes in the stimulus to the movement of the eye in degrees. The dotted line represents a mean-curve showing the trend of the data from Figure 3. It is clear that a disparity in fixation is again demonstrated, that the magnitude of the movement is less than the stimulus, and that the magnitude of disparity increases as the stimulus increases.

‡ Dr. Gordon L. Walls, of the University of California, provided this filter.

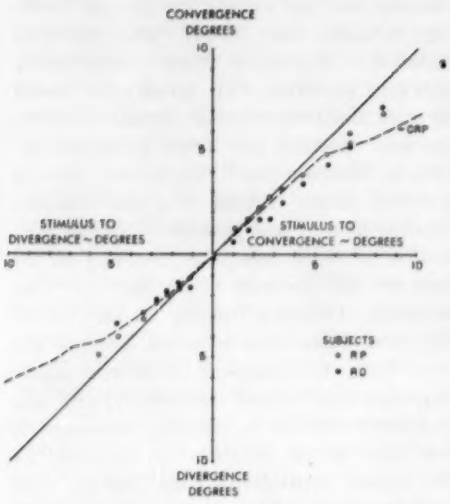

Fig. 4.—Summary of data from the Maxwell spot experiment. Measurement of the discrepancy between the angle of intersection of the lines of sight and the angle of convergence of the targets for two observers fixating on a vertical line at 1 meter distance through various prisms. The dotted line represents a mean of the data in Figure 3, which has been arbitrarily superimposed in this Figure at the origin of coordinates. The points are the means of five measurements of the eccentricity of fixation for each of two subjects. The origin of coordinates represents the convergence required for fixation at 1 meter, and all other convergence and divergence values are relative to this zero position.

Despite the differences in observers, testing distances, target size, and luminance and the crudeness of the Maxwell spot measurement, the data are remarkably similar from the two types of experiments. The discrepancy at the larger values of convergence are probably due to the underestimations of eccentricity in the experiment with Maxwell's spot, but artifacts in the electrical measurement of the eye movement cannot be definitely excluded. Even with such artifacts, it is clear from the Maxwell spot experiment, however, that the angle of intersection of the lines of sight during a fusional movement may be different from the convergence angle of the targets by as much as 1.7 degrees. This is the order of magnitude reported by Tani, Ogle, Weaver, and Martens,[5] if somewhat smaller than the maximum values reported by Peckham,[6,7] Clark,[1,2] and Stewart,[3] using optical recordings.

While the present experiments cannot exclude the possibility of a shift in the eyes in the orbit during the vergence movement, they do show that fixation disparities of the magnitude of 1.7 degrees do occur during a fusional movement with centrally fixed targets. Hence, the necessity Tani, Ogle, Weaver, and Martens felt for postulating an ocular position shift in the orbit is subject to question.

C. Comment.—The above results shed some new light on a very old experiment. Wheatstone (1852) pointed out that, after unification of half-views in his mirror stereoscope, if the arms of the stereoscope were rotated so that the convergence required for unification was increased the perceived size and distance of the unified halfview were reduced.[23] Helmholtz[24] and others,[25,26] have regarded this as evidence of depth discrimination arising from an increase of convergence per se. This interpretation seems unlikely, since the effect never has been reported by persons—such as myself—whose eyes converge quite adequately but who do not have stereoscopic vision in the strict sense that Ogle[8] uses the term. A more reasonable explanation for the Wheatstone effect is that as the stimulus to convergence increases the eyes rotate, but the magnitude of the rotation of the eyes is less than the stimulus to the movement. As a consequence, the retinal images of the two half-views are now stimulating disparate (i. e., noncorresponding) retinal areas and the perceived target will be displaced forward in space an amount determined by the point of intersection of lines projected from the stimulated retinal area through the respective nodal points of the two eyes. This perception of depth is a pure stereoscopic effect and will have associated with it a reduction in perceived size of the target, according to the law of the visual angle which Emmert[27] established

for the size of the projected afterimage.§

Another subjective manifestation of the failure of the lines of sight to intersect at the object viewed during prism vergence should be a change in the stereoscopic sensitivity when viewing some such device as Howard's [29] apparatus through base-in and base-out prisms. It is known that the locus of maximum stereoscopic sensitivity has a fixed relation to the point of intersection of the lines of sight,[8] and presumably the stereoscopic sensitivity rapidly decreases on either side of this locus. As a prism, base-in or base-out, is introduced, the present findings show that the point of intersection of the lines of sight will move in or out and with this movement the position of the locus of maximum stereoscopic sensitivity will also move in or out. Since the position of the measuring apparatus remains fixed, however, the measured stereoscopic acuity should show a rapid decrease through use of the base-in or base-out prism. In 1944 Fry and Kent [30] demonstrated that such a decrease in stereoscopic acuity through use of base-in and base-out prisms does in fact occur. The individual differences obtained in their experiments would be interpreted in the above light as individual differences in the amount of disparity between the angle of intersection of the lines of sight and the angle of convergence of the targets during vergence. The wide range of individual differences in this latter respect can be inferred from Tani, Ogle, Weaver, and Martens' recent review of the literature.

The fact that the eyes respond only partially to a change in the stimulus to vergence movements emphasizes the importance of repeating a large number of experiments [31-34] on the zone of single vision under conditions where it should be possible to determine the angle of the intersection of the lines of sight, rather than just the stimulus to convergence. The theoretical position derived from the original experiments may require considerable revision when examined in this new way.

Summary

Measurements of the horizontal movements of the eyes in terms of the ocular rotational potential were recorded when base-in and base-out prisms were suddenly introduced or removed before one eye. The results showed that there is a disparity between the record of the eye position and the magnitude of the stimulus to the movement. The recorded magnitude of eye movement was always smaller than the stimulus, and the magnitude of the disparity (several degrees) appeared to increase as the stimulus increased. The similarity between such responses as obtained by an electrical recorder of eye position and those obtained with an optical recorder make it extremely unlikely that the effect can be explained as an anterior-posterior and/or a nasal-temporal shift of the eyes in the orbits during vergence movements.

The possibility that the lines of sight intersect at an angle which is smaller than the angle of convergence of the targets predicts entoptic evidence of underpointing during a vergence test with a single line on a dichroic background. Approximate measurements of the magnitude of underpointing actually obtained in such experiments are in good agreement with data obtained with the electrical recorder of eye

§ A similar effect can be demonstrated during prism vergence testing. As prism base-out is introduced, the target gets smaller and appears closer to the observer; as prism base-in is introduced, the target gets larger and appears farther away. The magnitudes of the perceived changes in image position and size can be calculated from equations derived from the geometry of the theory:

$$\Delta D = aD/P \quad (1)$$

and

$$\Delta S = Sa/a+P \quad (2)$$

where a is the linear disparity projected on to the target plane; D is the distance of the target; S is the physical size of the target; P is the interocular distance, and ΔS and ΔD are the perceived changes in size and distance, respectively. In recent experiments in which the amount of convergence was held rigid, it has been shown that the measured changes in perceived size and distance agree accurately with those predicted by these theoretical equations.[35]

position. This suggests that an actual disparity exists during vergence test between the angle of intersection of the lines of sight and the angle of convergence of the targets. This in turn readily explains perceptual distortions which occur during prism vergence tests as well as the effect of base-in and base-out prisms on stereoscopic sensitivity.

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Serum Proteins and Total Glucosamine in Diabetic Retinopathy and Glomerulosclerosis

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The increase in the life expectancy of diabetics which has occurred in the post-insulin era, and which has been further augmented by the general advances in the understanding and treatment of metabolic disorders, has led to an increase in the degenerative complications of diabetes. Such is apparently the case with diabetic retinopathy, a complication which intimately concerns the ophthalmologist. Friedenwald [2] and Vogelius,[3] among others, have reported a marked increase in the incidence of retinopathy in the patients they studied, and, although there is still a good deal of controversy regarding the relationship of retinal disease to the degree of control of blood sugar, it is now generally accepted that the most important factor is the duration of the diabetes. The histopathological picture of diabetic retinal disease has been well defined by the excellent studies carried out by Ballantyne and Loewenstein,[4] Ashton,[5] and Friedenwald,[2,6] and the diabetic microaneurysms show a striking similarity in staining characteristics to diabetic renal lesions. Studies by Ashton [5] and Henderson, Sprague, and Wagener [7] have shown a very high degree of correlation in the occurrence of renal and retinal disease. Well over 80% of patients with diabetic glomerulosclerosis were clinically found to have retinopathy to some degree.[7] An even higher correlation was found at postmortem examination. Thus there is a close relationship between the Kimmelstiel-Wilson nephropathy [8] and diabetic retinopathy. They are both specific lesions of a vascular nature occurring in diabetes mellitus, and it is probably valid to assume that the lesions have a common histogenesis.

Clinical,[9-12] histological [13,14] and experimental [15-20] evidence has been accumulating which would tend to support Friedenwald's concept [21] of an adrenal cortical hyperactivity being implicated in the pathogenesis of these retinal and renal lesions. Reports [22-25] have recently appeared which indicate that both insulin and cortisone are involved in mucoid metabolism. It would appear, therefore, that an important pathway leading to the production of these lesions is a disturbance of mucoid metabolism induced by diabetes and exacerbated by adrenal hyperfunction.

In order to investigate the aforementioned hypothesis in the early stages of lesion formation, the composition of the serum proteins, separated by paper electrophoresis, and total glucosamine levels have been measured in a group of normal persons and diabetic patients with and without retinopathy. Although attempts at the experimental production of diabetic retinopathy by prolonged cortisone administration have been unrewarding, the yield of renal lesions closely resembling the typical Kimmelstiel-Wilson lesions has often been very

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high. Assuming a similar pathogenesis for both the renal and retinal lesions of diabetes, the sera of two groups of alloxan-diabetic rabbits were studied in the same manner. One group was kept as the diabetic control; the second was given cortisone intramuscularly over a three-week period.

Methods

1. *Experiments on Human Sera.*—The normal controls were derived from hospital personnel of the Wilmer Institute. Diabetic patients were drawn from the diabetic clinic of the outpatient department of the Johns Hopkins Hospital. The majority were on insulin therapy, but the disease in some was controlled by diet alone. All of the patients had been followed for varying periods of time (several months to many years) in the diabetic clinic. Their diabetic state was considered to be under satisfactory control, and only those persons who were in reasonably good health and suffered from no other clinically detectable disease were chosen for this study. They were all carefully examined under mydriasis (10% phenylephrine [Neo-Synephrine] hydrochloride and 1% cyclopentolate [Cyclogyl] hydrochloride) and were classified ophthalmoscopically into those who showed no evidence of diabetic retinal disease (non-retinopaths) and those who had retinopathy (retinopaths). The degree of retinopathy varied in severity from one or two microaneurysms to retinitis proliferans (two cases).

Approximately 10 ml. of blood was drawn from each person, and the blood was allowed to clot for two to three hours at room temperature. After removal of the clot, the serum was centrifuged for 10 minutes. A fraction of the serum was used for the electrophoretic studies, the remainder was stored at −20 C and subsequently analyzed for total glucosamine content.

2. *Experimental Studies on Rabbits.*—Male albino rabbits weighing approximately 2 kg. were employed. Their diet consisted of Sherwood rabbit pellets with no added vitamin B_{12} or chlortetracycline (Aureomycin). Ten milliliters of blood was taken from each rabbit by cardiac puncture and treated as for human serum. Each was then given a total of 400 mg. of alloxan intravenously in divided doses, and the urine was tested on two successive occasions. The urine was obtained by catheterization and was tested with Benedict's reagent (qualitative). Only those rabbits whose urine was 2+ or higher on both occasions were included in this study. As the experiment progressed, the urine samples were rechecked at weekly intervals in a similar manner.

Approximately eight days after the last intravenous injection of alloxan, 10 ml. of blood was again drawn from each animal and the sera were subjected to analysis as above. The animals were then divided into two groups. The first (eight rabbits) served as diabetic controls; the second (nine rabbits) was given a daily intramuscular injection of 8.3 mg. of cortisone acetate (Merck) for 21 days. Ten milliliters of blood was drawn from every rabbit at weekly intervals for analysis.

At the end of the 21-day period, all the surviving rabbits were killed and autopsied and the kidneys were removed for histological examination. The survival rate was good in the first group; seven of eight rabbits were alive after four weeks. In the second, six rabbits survived the full 21 days of cortisone administration.

3. *Paper Electrophoresis.*—The method of von Frijtag Drabbe and Reinhold[26] for separation of serum proteins by paper electrophoresis was employed with some modifications. A plastic Electrorheophor cabinet (Brinkmann Instruments, Inc.) was used for the electrophoresis. Strips of 1 mm. width rather than 2 mm. were used to apply the serum samples. The electrophoresis was run at 150 volts and 5 ma. for 16 hours at 4 C. After removal of the plastic bridges and blotting of the strip ends, the strips were dried for 10 minutes at 50 C, then

removed from the bridge and heated 10-15 minutes at 100 C. The paper strips were stained for 15 minutes in Amido black solution, 1.0 gm. of Amido black dye (Amido Schwarz 10B) dissolved in 1 liter of a solution prepared by diluting 100 ml. of glacial acetic acid to 1 liter with methanol. They were then destained by soaking for 10 minutes in the first cylinder of destaining solution, followed by 70 minutes in a second and third cylinder of destaining solution. The strips were then dried at room temperature and read directly in a densitometer (Photovolt Corp.). The optical density readings were directly plotted, and a continuous curve was drawn through the points as shown in Figure 1. The surface area of each protein fraction was measured with a planimeter, and the relative per cent of each fraction was calculated.

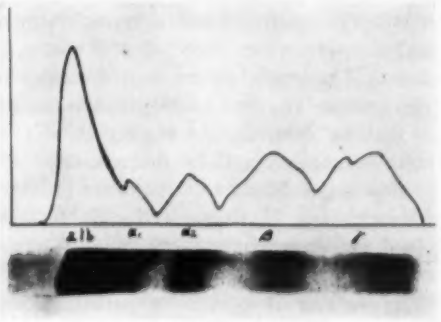


Fig. 1.—Plot of optical density versus position on the paper strip for the stained serum protein paper electrophoresis chromatogram shown at bottom. Migration was from right to left (cathode to anode).

4. *Total Serum Glucosamine Determinations.*—Samples of serum (0.08-0.10 ml.) were hydrolyzed in 1 N HCl in a 1 ml. final volume in sealed Thunburg tubes at 100 C for 24 hours. Glucosamine was then determined by a slight modification of the Blix-Elson-Morgan method.[27] These conditions were found to give maximal glucosamine levels in sera. A 2.25 N sodium carbonate solution instead of 1.25 N was used in order to neutralize the acid. Samples were analyzed in triplicates, which agreed within ±5%.

Results

1. *Studies on Human Sera.*—The relative percentages of albumin and α_1-, α_2-, β-, and γ-globulins determined on the human sera of 14 normal controls, 17 diabetic nonretinopaths, and 20 diabetic retinopaths are summarized in Table 1. The only statistically significant increase was in the α_2-globulin level of the diabetics with retinopathy. The mean α_2-globulin level in the retinopaths (14.2%) was significantly higher than either the normal or nonretinopath values, the latter two being almost identical (12.3% and 12.0%, respectively). The only other statistically significant change was a drop in the α_1-globulin in this latter group. The validity of this decrease is questionable, since the α_1 fraction is very small and there is considerable overlapping from the albumin fraction by tailing.

The levels of total serum glucosamine in the same sera are summarized in Table 2. A statistically significant increase was found in diabetics both with and without retinopathy. However, there was no statistical difference between the two diabetic groups.

2. *Studies in Rabbits.*—In Table 3, the results of serum protein studies in a group of alloxan-diabetic rabbits over a period of four weeks are summarized. The levels of the various protein fractions remained remarkably constant over this period, and the values of each fraction after four weeks of diabetes agree very closely with the values obtained prior to production of the diabetes. There was no statistically significant increase in the α_2-globulins, although this value was lower at three weeks and there was a correspondingly higher percentage of albumin.

Pathological examination of the kidneys from this group revealed the complete absence of lesions in all except one case, in which several glomeruli showed small granular deposits which may have been the result of postmortem autolysis.

The results of the serum protein studies in the second group of diabetic rabbits, given intramuscular cortisone, are summa-

TABLE 1.—*Serum Protein Patterns in Normal Patients and Diabetic Patients With and Without Retinopathy* *

	Protein (per Cent of Total)				
	Albumin	Globulins			
		α_1	α_2	β	γ
1. Normal (14)	37.1±3.4	7.8±1.4	12.3±1.7	17.1±1.8	25.8±3.9
2. Diabetics without retinopathy (17)	35.8±4.5	6.3±1.8	12.0±1.9	18.2±1.7	27.8±4.9
3. Diabetics with retinopathy (20)	34.4±4.3	7.4±1.1	14.2±2.7	17.5±2.4	26.6±4.2
Statistical significance					
$P_{1,2}$	>0.3	<0.02	>0.5	>0.05	>0.2
$P_{1,3}$	>0.05	>0.3	<0.05	>0.5	>0.5
$P_{2,3}$	>0.3	<0.02	<0.01	>0.3	>0.4

* Values expressed as mean± standard deviation. The numbers in parentheses refer to the number of patients in each group.

TABLE 2.—*Comparison of Total Serum Glucosamine Levels in Normal Patients and Diabetics With and Without Retinopathy*

	Normals (1)	Diabetics		
		Without Retinopathy (2)	With Retinopathy (3)	All Diabetics (4)
Number of cases	10	19	17	36
Mean, mg. per 100 ml.	113	139	127	133
Range	92-145	111-179	93-166	93-179
Standard deviation	15.3	20.8	17.6	20.1
Statistical significance				
$P_{1,2}$	<0.01	$P_{1,4}$	<0.01	
$P_{1,3}$	<0.05, >0.02	$P_{3,4}$	>0.05	

TABLE 3.—*Changes in Serum Proteins in Alloxan-Diabetic Rabbits*

Duration of Diabetes, Wk.	Protein (per Cent of Total)				
	Albumin	Globulins			
		α_1	α_2	β	γ
Normal (8)*	33.6	7.0	14.2	21.7	23.6
1 (8)	34.4	6.4	13.3	20.8	25.1
2 (8)	34.3	7.2	14.0	19.8	24.7
3 (7)	29.3	7.3	16.8	18.8	23.8
4 (7)	30.8	7.4	14.4	20.9	26.6

* Number of animals given in parentheses.

TABLE 4.—*Changes in Serum Proteins in Alloxan-Diabetic Rabbits Given Cortisone Intramuscularly*

	Protein (per Cent of Total)				
	Albumin	Globulins			
		α_1	α_2†	β	γ
Normal (9)*	35.1	6.7	13.3	20.4	24.6
Diabetic for 1 wk. (9)	32.0	7.2	14.0	20.9	26.0
Cortisone given					
1 wk. (9)	34.5	7.2	15.4	20.6	22.3
2 wk. (9)	37.9	7.5	16.1	19.4	19.1
3 wk. (6)	30.0	6.4	16.7	22.7	24.3

* Number of animals given in parentheses.
† Statistical significance of α_2-globulin changes: Normals vs. diabetics on cortisone, 1 week, P >0.1; 2 weeks, P <0.02; 3 weeks, P <0.05.

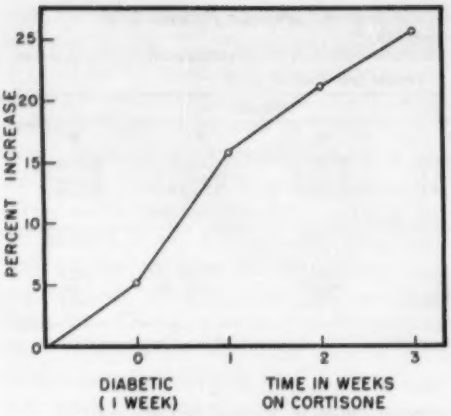
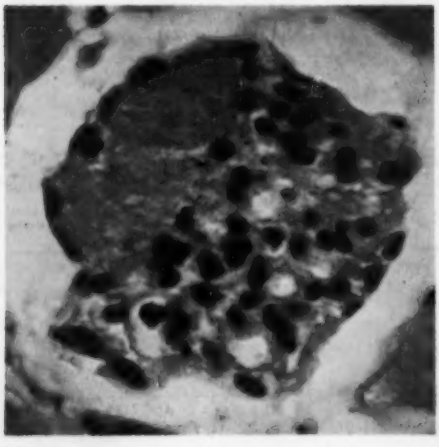


Fig. 2.—Changes in the α_2-globulin protein fraction of alloxan-diabetic rabbits given cortisone.

rized in Table 4. The initial values agreed very closely with those observed for normal levels in the first rabbit group. It is to be noted that following administration of cortisone the α_2-globulin values showed a steady increase—from an initial value of 13.3% to 15.4% after one week of cortisone, to 16.1% after two weeks, and to 16.7% after the third week. The increase was statistically significant after 14 days. These results can be seen more clearly in Figure 2, where the percentage increase over the normal is plotted graphically. There was no significant increase in any of the other fractions.

Fig. 3.—Rabbit glomerulus showing glomerulosclerosis similar to the Kimmelstiel-Wilson lesion.



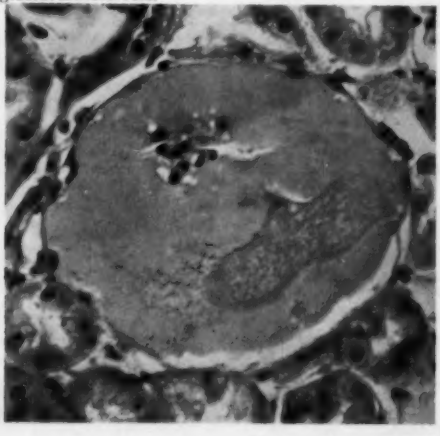
Pathological examination of the kidneys from this group revealed definite lesions in six cases (Figs. 3 and 4), an early lesion in one, and one that was equivocal. Autolysis was too far advanced in one specimen for an adequate pathological examination.

The mean value of total serum glucosamine in six of the sera in this group before alloxan injection was 89 mg. per 100 cc., and this rose to 94 mg. per 100 cc. in the sera from the same animals after they had been given cortisone for three weeks. The difference was not statistically significant ($P>0.4$).

Comment

The results of the present study indicate that diabetics with retinopathy have a significant elevation in their serum α_2-globulin levels, while in diabetic patients without retinopathy the α_2-globulin remains at normal levels. This study agrees well with those reported by other investigators,[28,29] who have found increases in the α_2-globulin fraction as the retinal and renal complications of diabetes appear and increase in severity. In our series, only 2 of the 20 retinopaths showed severe retinal changes ophthalmoscopically, and in both of these persons the α_2-globulin value was elevated, to 17% and 20%, respectively. Kidney-function tests in all the diabetic subjects

Fig. 4.—Rabbit glomerulus showing severe glomerulosclerosis.



studied in this series were normal, and none showed any evidence of albuminuria.

The human α_2-globulin fraction has been reported to contain 42% of the total serum glycoprotein.[30] Therefore a significant rise in this fraction might be because of an increased glycoprotein content. Such an increase should be reflected by a concomitant elevation in the serum glucosamine level, this amino sugar being one of the major constituents of these mucosubstances. Although a significant elevation in glucosamine was found in our series of diabetic patients, we were unable to demonstrate any difference in the glucosamine level between retinopaths and nonretinopaths. A similar increase, of 18%, was reported by Berkman [31] in a study of total serum glucosamine levels in a group of patients with uncomplicated diabetes compared with nondiabetic controls. It thus appeared that the larger increases he observed in both total serum glucosamine and total protein-bound polysaccharide in the sera of patients with advanced degenerative vascular disease occurred at a later stage in the development of vascular lesions than were present in the patients included in our study.

In the rabbit experiments, seven of the nine animals receiving a three-week course of intramuscular cortisone developed renal lesions of the Kimmelstiel-Wilson type, and their serum α_2-globulin values were significantly higher than both their preexperimental normal levels and the levels in the diabetic control group, but there was no significant difference in the glucosamine levels of the two groups.

The experimental production of renal lesions similar to those seen in human diabetic glomerulosclerosis and the increased α_2-globulin levels in both animal and human diabetics suggest a common pathogenesis in the development of the diabetic renal and retinal lesions and is further evidence that this experimentally produced disease is closely allied to the disease occurring in man.

Summary

Diabetics with retinopathy have a significantly elevated serum α_2-globulin, while the α_2-globulin level in diabetics without retinopathy remains the same as in normal controls.

Alloxan-diabetic rabbits, after a three-week course of cortisone injections, showed a significant elevation of serum α_2-globulin level. At least 80% of these rabbits developed renal lesions of the Kimmelstiel-Wilson type.

The serum glucosamine levels were elevated in all diabetic patients, but no statistically significant difference was found between diabetics with and those without retinopathy. There was no statistically significant increase in the serum glucosamine levels of the alloxan-diabetic rabbits after a three-week course of cortisone administered intramuscularly.

Mr. P. Roane gave technical assistance in the glucosamine analyses; Dr. J. Duke aided in the pathological examinations, and Dr. E. C. Brown Jr. referred the diabetic patients.

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Aqueous Humor Flow

The Effects of a Ganglionic Blocking Drug, Pentolinium, on Certain Aspects of Aqueous Humor Dynamics

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Drugs which have the property of blocking transmission in autonomic nerve ganglia are at present being employed widely in the treatment of arterial hypertension. The agents most commonly employed are of the tetraethylammonium and the methonium groups. They act either by preventing depolarization of the cellular membrane of the postganglionic neuron or by producing a prolonged depolarization with an associated absolute refractory state. During the blockade induced in this manner autonomically innervated structures of both the sympathetic and the parasympathetic nervous systems do not respond to preganglionic stimulation but remain sensitive to postganglionic stimuli. Thus the sympathetic tone of small arterioles is depressed, resulting in a fall in peripheral vascular resistance and in blood pressure. Associated with this effect are other evidences of autonomic blockade such as interference with bladder and bowel motility, dryness of the mouth, inhibition of sweating, mydriasis, interference with accommodation, and impotence in the male. Ophthalmologists are becoming familiar with instances of regression of hypertensive retinopathy, often of the more severe grades, following the use of these drugs.[1]

This report deals with the effects of one of the newer methonium drugs, pentolinium (pentapyrrolidinium), on some aspects of intraocular fluid dynamics.

Methonium drugs consist of a series of alkyl groups linked at either end to an unsaturated nitrogen atom. Thus, hexamethonium contains six methyl groups at the core of the molecule and six additional methyl groups attached to nitrogen atoms at the two poles (Fig. 1).

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From the Department of Ophthalmology, Queen's University Faculty of Medicine.

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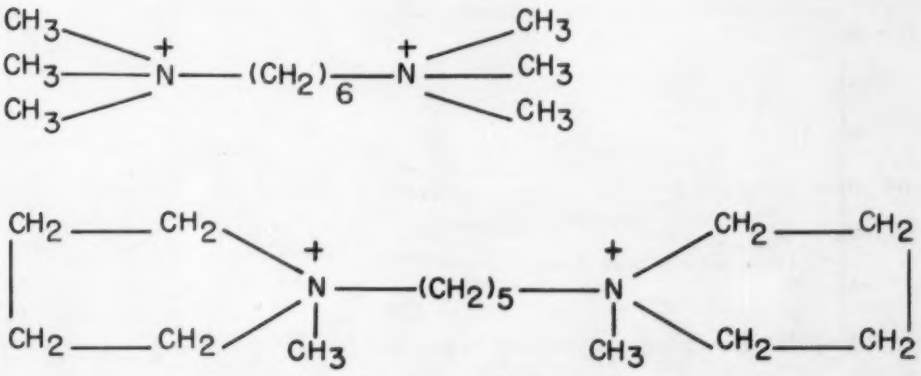

Fig. 1.—Structural formulas of hexamethonium (above) and pentolinium tartrate (pentamethylene-1,1'-bis-[1-methylpyrrolidinium bitartrate]) (below).

Pentolinium was first synthesized in 1952,[2] and its pharmacology and effects on blood pressure have been reported by Wien and Mason,[3] Smirk,[4] and Freis et al.[5] It was first marketed as M & B 2050A but is currently distributed under the trade name Ansolysen. The molecule consists of five methyl groups linked through a nitrogen atom at each extremity to pyrrolidine rings. Each nitrogen atom is joined to a single methyl group. While pentolinium was initially produced as a di-iodide salt, Ansolysen is a bitartrate. The compound when administered by mouth is five times as potent as hexamethonium and has one and one-half times the duration of action of hexamethonium. The hypotensive effect has been found to last 6 to 36 hours. The side-effects are similar to those of hexamethonium and are related primarily to parasympathetic blockade, e. g., constipation and dysuria.

I became interested in the ocular effects of this drug while carrying out tonographic studies on hypertensive patients being treated with pentolinium. One finds almost regularly when carrying out tonographic measurements that the starting pressure (P_1) in the second eye is from 1 to 4 mm. of mercury lower than in the first eye. There appears to be some mechanism whereby through increase in facility of outflow or decrease in rate of aqueous formation a fall in intraocular pressure in the second eye results. In subjects who were under treatment with pentolinium, however, the contralateral lowering of intraocular pressure was no longer observed, and the opening pressure in the second eye was found frequently to be slightly higher than that in the first.

Figure 2 illustrates the calculated values for ΔP, the difference in P_1 between the first and second eyes after a standard four-minute tonography, on two successive days. On the control day (solid line) tonographic determinations were made at roughly two-hour intervals between 8 a. m. and 10 p. m. On the following day the patient was given 20 mg. of pentolinium tartrate by mouth and a similar set of determinations was made. The value for ΔP was consistently lower and, indeed, negative through most of the experimental day, since the opening pressure in the second eye, rather than being lower, became higher than that of the first eye. The findings illustrated in Figure 2 are typical of those observed in a series of 12 patients.

There is extensive evidence that many varieties of trauma to an eye result in a lowering of intraocular pressure in the contralateral eye as a result of inhibition of aqueous secretion. This effect has been referred to in literature as the "ophthalmotonic consensual reaction." Thus Larsson,[6] Linnen,[7] and Leplat[8] observed a fall in contralateral intraocular pressure after

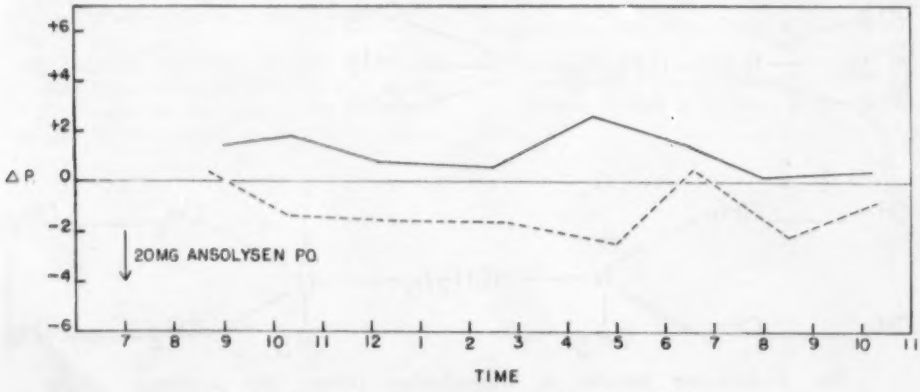

Fig. 2.—Change in ΔP after administration of pentolinium.

experimental ocular contusions. Barany and Wirth [9] noted an occasional cessation of flow of aqueous in the opposite eye following anterior chamber paracentesis. Nagata and co-workers [10] noted that the consensual fall in intraocular pressure could be inhibited by prior administration of tetrathylammonium chloride.

It seems reasonable to judge that the consensual effect of tonography results from a neural or neurovascular influence. Since this response becomes altered with the use of a ganglionic blocking drug, one or another division of the autonomic nervous system may be implicated in this effect. Prijot and Stone [11] have succeeded in blocking the consensual effect of ocular compression by atropine and conclude that the parasympathetic system predominates in effecting contralateral ocular reactions.

I proceeded next to investigate by tonography the effect of pentolinium on the rate of aqueous flow. Figure 3 indicates comparative flow rates in patients who were given 10 and 20 mg. of pentolinium tartrate on two successive days and in whom tonographic determinations were carried out at irregular intervals up to nine hours after administration of the drug. Calculations were made from tonographic recordings obtained using a Mueller electronic tonometer linked to the amplifying and recording systems of a Leeds and Northrup Model B Speedomax Recorder. Friedenwald's 1954 calibration scale [12] was used to obtain values for P_0 and Linner's value of 11 mm. of mercury was employed for episcleral venous pressure.[13] Calculations of flow were made with use of Grant's equations [14] and compared with a control level arrived at by averaging values from repeated tonograms performed on three days prior to administration of the drug. Figure 3 indicates results obtained in 9 of 18 patients investigated in this manner. In 17 of these (94.4%) a profound fall in aqueous flow rate occurred which persisted up to a period of nine hours. In some instances the drug appeared to be

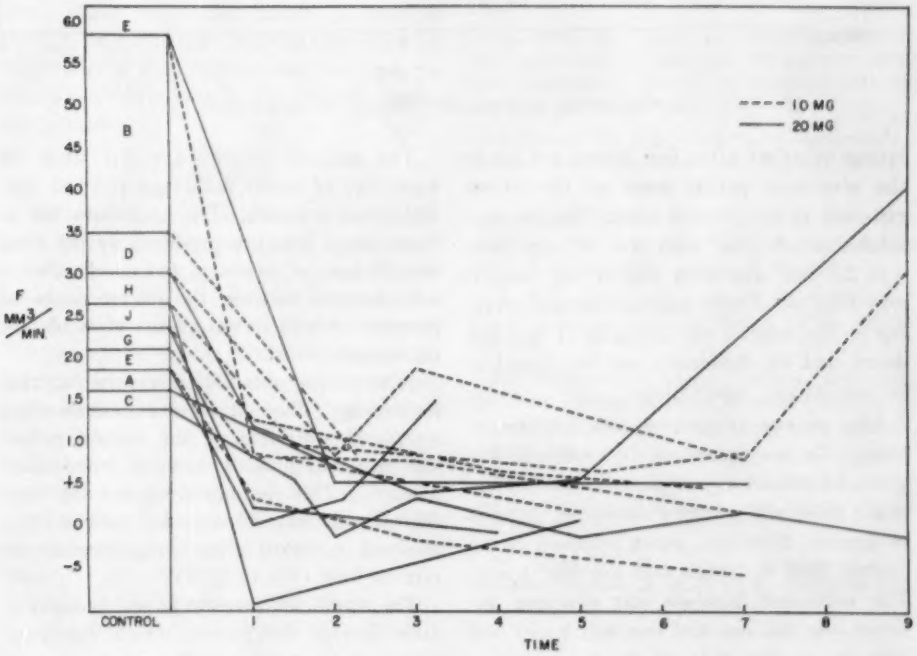

Fig. 3.—Aqueous flow rates after administration of pentolinium.

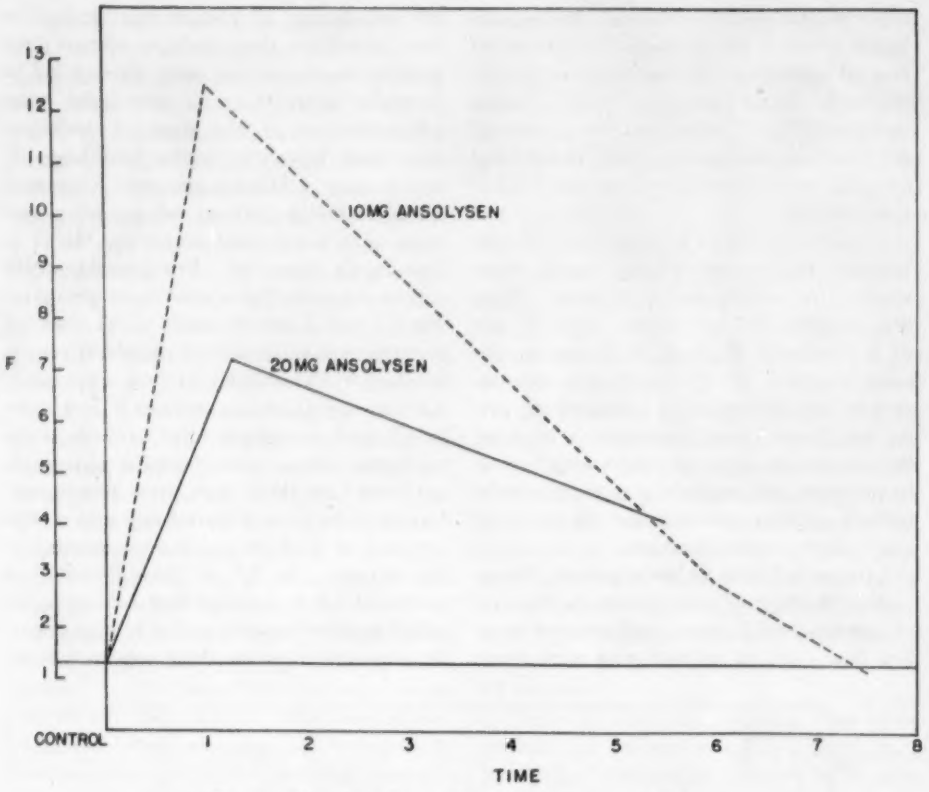

Fig. 4.—Unusual aqueous flow response to pentolinium.

losing its effect after five hours, but up to the nine-hour period none of the values returned to the control level. The average inhibition of flow with the 10 mg. dose was 70.13%, and with the 20 mg. dose it was 77.07%. There was considerable overlap in the relative effectiveness of the two doses, and the difference was not found to be statistically significant.

One patient (Figure 4) reacted anomalously. On two successive days when he was given 10 and 20 mg. of pentolinium tartrate orally there was a very pronounced increase in aqueous flow rate, which returned to the control level by seven and one-half hours. The maximum increase was observed between one and one and one-half hours and with the smaller dose of the drug.

The patients selected for this study all were free of ocular pathology and had normal blood pressure. The maximum fall in mean blood pressure produced by the drug was 20 mm. of mercury, and no correlation was detected between the degree of blood pressure reduction and extent of inhibition of aqueous flow.

A surprising observation was the fact that the average fall of intraocular pressure when compared with that of the control period was only 1.57 mm. of mercury, a decline of 12.55%. This is explained by the fact that the facility of aqueous outflow (C) declined in almost direct proportion to the rate of flow (F) (Fig. 5).

The significant conclusion which one may draw is that the factors which determine resistance to aqueous outflow in the normal

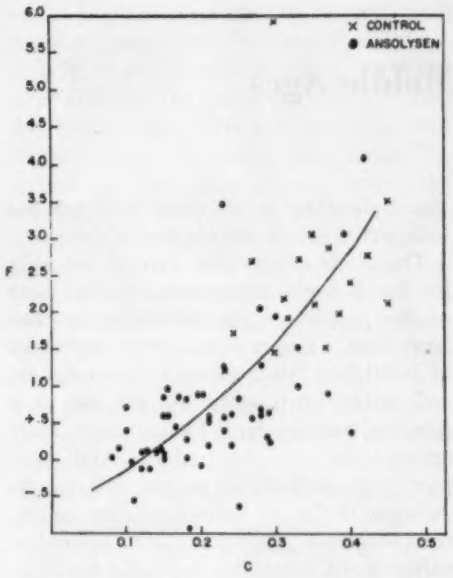

Fig. 5.—Aqueous flow rates and outflow facility after pentolinium.

eye are dynamic rather than static and may vary within broad limits in a short period of time. These rapid fluctuations of outflow facility may be more readily explained by innervational and vascular factors than by anatomical variations in the aqueous drainage passages.

Comment

These studies of the effects of a ganglionic blocking drug on some features of aqueous humor dynamics in normal human eyes support the concept that neurovascular factors are strongly at play in producing reflex consensual ocular effects. Evidence has been presented that the drug studied causes a profound fall in the rate of aqueous flow and that this fall is compensated almost fully by a corresponding decrease in the facility of aqueous outflow. This appears to represent a homeostatic mechanism for the maintenance of a stable intraocular pressure.

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Ophthalmology During the Middle Ages

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Like all other branches of medicine, ophthalmology has made such fantastic strides during the last 100 years that the preceding millennia appear to us telescoped into a jumble of ignorance, incompetence, and superstition. The Renaissance prepared the European spirit for the subsequent blossoming of modern fundamental science during the golden age of science, the 17th and 18th centuries, which, in turn, led to the phenomenal development of the applied sciences since 1800. A closer scrutiny of the earlier state of science and of medicine, in particular before 1500, permits us, however, to discern that our subject during the Dark Ages had its ups and downs, its progresses and its regressions. Let us see what lessons may be drawn from history!

What are the sources of medieval ophthalmology? Medical books and manuscripts, letters and reports, and numerous legal and other documents relating to the practice of ophthalmology. During the middle ages, i.e., after the decline and fall of the Western Roman Empire, the center of Caucasian civilization moved eastward and the people with the new religion of Mohammed dominated the known world not only politically but intellectually and culturally. Not only was Arabic the language of the peninsular Arabs, but it gradually replaced (1) the Egyptian or Coptic language, (2) the Persian language, and (3) the Syriac or Aramaic language, a close relative of Hebrew, current in Palestine and the Near East since the time before Jesus Christ. Only the Persian language subsequently made a comeback and is in current use to this day.

The Arab culture was carried not only by the Bedouin conquerors but by most of the peoples of the Mediterranean and Near East. In spite of temporary outbreaks of fanaticism, Islam tolerated other religions and, unlike Christianity, did not aim at a spiritual monopoly. Thus, one finds amongst the inhabitants of the Arab Empire great numbers of people adhering to Judaism, to the old Persian religion, and to the numerous orthodox and heterodox varieties of Christianity, especially the Nestorian creed, which reached far into Asia after having been driven out of the Byzantine Empire. The people under Arab rule used Arabic almost exclusively as their literary language—as the Western nations wrote in Latin—but the variety of religion, philosophy, and tradition in general and the absence of such rigid dogmatism as was imposed upon the Western worlds by the church kept fundamental and applied science in a livelier state of development and did not shun experiment and observation, in contrast to the stagnation prevailing in Europe under the Schoolmen. There was a great deal more empiricism in Arab science, but most characteristic for the Arabic spirit seems to be its systematic, one might say encyclopedic, approach to the subjects under study.

Between the years 800 and 1400 incomparably more manuscripts were written in Arabic than in Latin, Greek, and other European languages together. There were 36 libraries in Bagdad alone before its destruction by the Mongols, one containing 80,000 volumes. The library in Cordoba contained 600,000 volumes; that in Cairo, 2,000,000. Substantial portions of these libraries are still in existence, or their treas-

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ures, despite wars and conquests, have found a repository in European libraries, especially in the Escorial in Spain, the Vaticana in Rome, the Laurentiana in Florence, the Bibliothèque Nationale in Paris, and others. Arabic language and script are known to few Westerners; hence the knowledge of the contents of these manuscripts is piteously fragmentary. An important Arabic medical codex in the Laurentiana had not been opened since 1740, when a German professor consulted it about 1900. During the last 100 years some of the most famous Arab scientific authors have been edited in the original Arabic—a few in England, several in Egypt and in India.

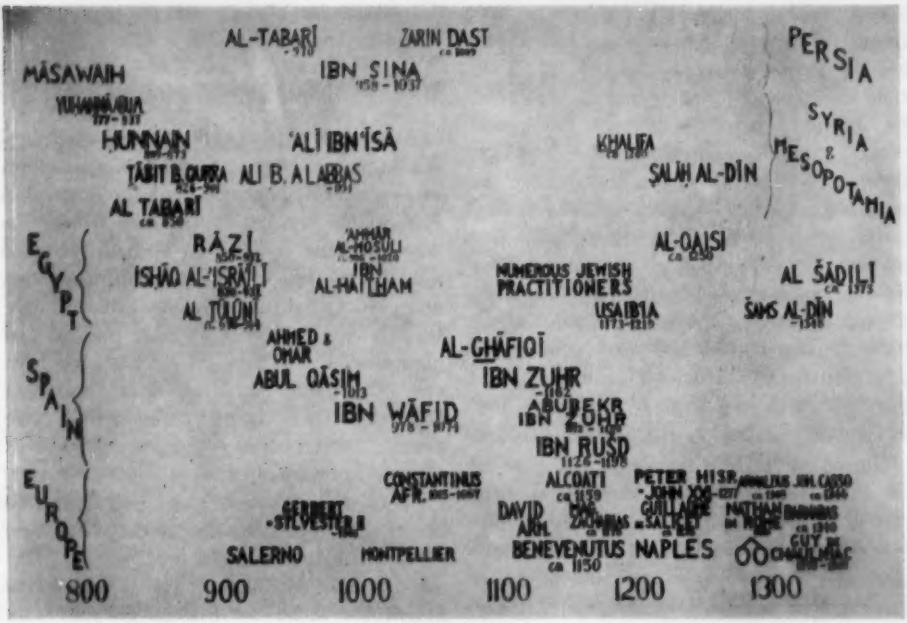
During the middle ages the knowledge of the Arab language was a little wider spread among Europeans. Especially, Jews endowed with linguistic talent had no reluctance to travel across what would be called nowadays an iron curtain. In reality, there was as much, if not more, traffic between Islamic and Christian countries as there is now between the capitalist and the communist domains. Cultural exchange was undoubtedly most significant in the field of commerce and also in regard to the practical acquisition of technical skills. In the case of books, it was not the difficulty of exporting Arab books to Western countries, but other factors, which hindered adequate translation: ignorance of the finer points of both Arabic and Latin, the absence of dictionaries, and, especially, the tendency of those most expert in the field to keep their knowledge to themselves. Add to this the generally low and barbaric level of medieval Latin and the numerous copying errors by ignorant and slatternly copyists and it becomes apparent why the medieval Latin translations of Arab authors are often desperately unintelligible and useless. Some of the best medieval translations are found amongst the less numerous translations from Arabic into Hebrew. But the modern historian will not be satisfied unless he may use as his sources the original Arabic texts translated by a team of philological and scientific experts.

Arab Ophthalmology

Around 800 there flourished a medical school of pre-Islamic origin in Giondisabur, in Persia. The pharmacist of the hospital, a Nestorian Christian by the name of Mesue Abu Johanna, moved to Bagdad, devoted himself to the practice of ophthalmology, and cured Khalif Harun Al-Rashid of ophthalmia; he received a monthly pension and high honors; we have no writings from his pen. The great physician Razi (850-932) cites in his "Continens" two practical compendia, collectively written by the guild of oculists at Bagdad, evidently Mesue's contemporaries. Mesue's son, Johanna Ben Mesue (777-857), was a prolific writer and composed a treatise, now lost, on the "Examination of Oculists." He is known as Mesue the Elder to distinguish him from a later, apocryphal, Mesue the Younger.

The most famous oculist, not only of the ninth century but cited as an authority throughout the middle ages, is Mesue the Elder's disciple Honein El Ibahdy (the apothecary) (809-873) of Bagdad, known in Latin translations as Johannitius. A Christian with knowledge of the Greek language, he wrote the "Work of Ten Books on the Eye." Tabit Ibn Qurra (836-901), a great physician and astronomer, member of a Christian sect, wrote "Improvement of the Seer and of Vision," but this has unfortunately been lost.

The first treatises on ophthalmology from the pen of eye specialists are likewise lost: El-Tuluni, the first Mohammedan among these authors and a famous practitioner in Egypt, worked on his book from 876 to 914. El-Tabari (†970), from northern Persia near the present Tehran, refers in his work "Hippocratic Treatments" to his own book on ophthalmology. In the chapter on eye disease of the "Hippocratic Treatments" he describes among other diseases a parasitic condition produced by small gnats,



Chronological synopsis of ophthalmological authors during the Middle Ages.

called "seekers of the eye," which attack the pupil. He gives a good description of snow-blindness and its treatment, a rare condition in warm climates, previously only mentioned by Xenophon in the "Anabasis," the march of his soldiers across the mountain ranges of Asia Minor. El-Tabari, whose work has not yet been thoroughly studied, was an eminent clinician but not a surgeon.

Another El-Tabari, son of a famous Jewish physician of Persia, Rabban El-Tabari, was converted to Islam and became court physician to two khalifs in the middle of the ninth century. His pupil was the great physician and prolific writer Razi (850-932), whose monumental work, the "Continens," is an excellent source for lost Greek writings; e. g., the best Greek description of operation for cataract by Antyllos is known only through Razi. The "Continens" is rather a collection of notes and observations, as Razi, according to Arab sources, never found the time to give it a definite form. In his second volume he deals with diseases of the eye. He recommends anesthetics against severe pain and a mercurial ointment for lice of the eye-lids. Visual disturbances of cerebral origin are accompanied by headache and tintinnus; involvement of the optic nerve is diagnosed by dilation of the pupil when the other eye is closed. His short textbook of general medicine, dedicated to Prince Mansur, was translated into poor Latin by Gerardus di Cremona in the 15th century. Razi cites, among others, his contemporaries Serafion, who wrote in the Syriac language, and Ishak El Israeli, a Jewish practitioner, who lived in Egypt to an age beyond 100 years (ca. 830-932).

During the 10th century Arab culture in Spain was already highly developed. Two brothers, Ahmed and Omar, sons of a physician of Cordoba, studied from 942-963 in Bagdad and returned as famous practitioners to Spain. Abul Qassim (†1013), the Albucasis of Western translations, another Spaniard, wrote a treatise on general medicine entitled "Explanation" viz., for those unable to compose prescriptions. Besides innumerable recipes, including remedies for

the eye, it contains a chapter on surgery, which was often separately copied.

Ali Ben Al-Abbas (†944) wrote one of the early comprenhensive treatises on general medicine, extant in many Arabic and Latin editions. This "Royal Book," shorter than Razi's "Continens," but longer than Razi's "Al-Mansuri," is a most systematic work, with the treatment of eye diseases well-organized according to the anatomic divisions of the eye. It was pushed into the background by the "Canon" of Ibn Sina (958-1037), in Latin Avicenna. The portion of the "Canon" which deals with the eye and its diseases is superior to its Greek sources; yet it brings nothing novel. None of these authors seems to have written about the eye from personal experience.

The oldest preserved treatise on ophthalmology per se is the "Memoir for Oculists" by Ali Ben Issa Al-Kahal, i. e., the oculist (†after 1010), the Jesus Hali of Latin translations. Of Christian origin, he lived in Bagdad. His work is being used by Arab physicians to our days. It has been preserved in 10 old manuscripts. Its contents signify a tremendous advance over Huneinn-Johannitius. During the following eight centuries, no equal book on ophthalmology has been written, and one may regret that there was not a more readable and, thus, more popular translation available in Europe.

Ammar Al-Mosuli was a famous practitioner, born in Mosul, who flourished in Egypt under Sultan Hakim (996-1020). His book "Selection of Eye Diseases" is one of the most original works. Besides the Arabic manuscript in the Escorial, there exists an excellent Hebrew translation by Nathan-ha-Meati in the library in Parma. Nathan, whose sojourn in Rome is documented for 1280, had also translated the "Canon" of Ibn Sina into Hebrew. A Latin treatise entitled "Magistri Davidi Armenici compilatio in libros de oculorum curationibus Accanomosali" exists in various manuscripts, the oldest of the 13th century. The same text is contained under the name "Canamusali" in a collection of surgical treatises printed in Venice 1500. It has little in common with Ammar's book except the name "Canamusali," evidently famous enough to be used as a fraudulent advertisement. To return to Ammar, his patients' histories are more detailed and also more unusual than anything described in the Greek literature or anywhere up to the 18th century. His descriptions of cataract operations are most dramatic and illustrate why Ammar invented the hollow needle for which he is famous. This enabled him to remove the cataract from the eye rather than just to push it away from the pupil ("couching"). His treatment became the standard procedure in the East, while the Spanish Moors polemized against it for a long time. He shows great consideration and feeling for the patient. Having travelled all across the Arab countries and North Africa, he attempts a medical geography of the cataract.

The Persians played an important part in the various interdynastic wars of the Arab empire. By the year 1000 they had started to resume the use of the Persian language and to create a Neo-Persian (Palehvi) literature. Eventually they made the Shiite heterodoxy of Islam their state religion and broke lose from the Bagdad khalifate. "Light of the Eyes" is the title of a Persian text of ophthalmology written in 1088 by Abu Ruh, known as Zarrin Dast, i. e., in Persian, the "Golden Hand." Like Hunein he still treats pathology and therapy separately, but he shows the same stage of progress as Ali Ben Issa and Ammar.

A Spanish work "Exact Consideration of the Illnesses of Vision," by Abul Mutariff Ibn Wafid, in Latin Abengefit (998-1074), vezir of the Emir of Toledo, has not come down to us. Another Spaniard, Muhamed Ibn Qassim El-Gafiqui is the author of the "Director" or the guide of ophthalmology (ca. 1100). Among the flower of science in the Spain of the 12th century, Ibn Zuhr, Latin Avenzoar (†1162), and Ibn Rushd, Averroes (1126-1198), were prominent

in natural philosophy and medicine, but their works contain only standard references to the eye. To Avenzoar's son, Abubekr Ibn Zuhr (1113-1199), or possibly to his grandson, has been attributed a lost treatise "De Cura Oculorum." A Latin manuscript found partly in Erfurt and in Metz is entitled "Congregatio sive liber de oculis quem compilavit Alcoati Christianus Toletanus A. D. 1159," written by Salomo filius de Arit Al-Coati, i. e., the Goth, possibly a converted Jew. According to the author, it was written partly in Toledo in Christian Spain and partly in Seville. That it was originally written in Arabic is shown by the remark "oculo hoc quod idem velit dicere quod fons" (by the eye which will mean the same as source), which makes sense only in the Arabic language, where *'Ain* means both "eye" and "source" or "well." Eventually an Arabic manuscript of part of Al-Coati's work was found in the Escorial.

In Egypt we find during the 12th century a galaxy of Jewish practitioners. Moreover, there was a school of Syrian oculists who had come from Damascus to Cairo. Most famous amongst them is Usaibiah, who was chief of the eye service of one of the hospitals in Cairo. We learn that there were special eye divisions in the hospitals of Cairo, Bagdad, Damascus, and elsewhere, an institution not to be found in Europe before 1800. Much of the above historical data originate from Usaibiah's "Classes of Physicians," one of the first treatises on the history of medicine.

Two books, written during the decline of the Arab empire, rank among the most learned ones. The "Book of the Sufficient (Al-Kafi) in Ophthalmology," by Khalifa of Aleppo, was written shortly after 1266 but before 1275, when it had already been copied. It is organized in tables, giving first the anatomy, then the treatment. The description of eye operations is given in punctilious detail. The book "Light of the Eyes," by Salah Addin, also a Syrian, one of the most voluminous texts, was written about 1296. We know nothing about the person of the author. Unlike the others, he discusses in the second book the theory of vision, going back to the "Optics" of Euclid.

From the middle of the 13th century on we find the literature of Arab medicine concentrated in Egypt. Al-Quasi, the "prince of the physicians" in Egypt, wrote a book "Results of Considerations Regarding the Treatment of Diseases of the Eye," a good compendium of little originality. Shams Addin (†1348) of Cairo, a scientist and physician but not a specialist, wrote a book "Discovery of the Dirt in Eye Disease" (the Arabic title forms a rhyme), a mediocre book, not free of superstitious ingredients. He describes for the first time a worm in the eye-lid (filaria), not again found before 1768 in a description by Bajou. Finally, the "Oculists' Help in Diseases of the Seeing Organ," written about 1375 by Al-Shadili, an Egyptian oculist, is an interesting work. It contains the nucleus of a comparative anatomy of the eye in animals, based on Aristotle, and also comparisons of the eye among the human races.

While Arab medicine in general showed little progress over Greek medicine, Arab ophthalmology was significantly advanced. The Arabs had special eye wards in their hospitals. They used soporific drugs like mandragora and opium for painful eye operations (not for cataract). While no special rules for cleanliness are mentioned, they seem to have kept their instrumentarium reasonably aseptic, as witnessed by the great number of successful operations performed. The introduction of the radical operation for cataract, its extraction rather than its mere dislocation, is their greatest achievement.

As regards the theory of vision, we meet numerous theoretical discussions in the Arab oculistic literature. Among the Greeks, Aristotle had recognized that the seeing process presupposed light-rays radiating from the object to the eye. But the Greek medical profession, especially Galen, adhered to the opposite idea, proposed by the majority of philosophers, like Plato, namely, that rays

went from the eye to the objects. Similarly, Al-Haitan Al-Basri, in Latin Alhazen, the author of the best Arabic treatise on optics, gives a correct theory of vision but was ignored by his medical contemporaries.

Collyria and ointments for the eye are as a rule more complicated than would be warranted even if one accepted the pharmacological claims for their constituents, the "simples." But the better authors keep at least away from the *Dreckapotheke*, with its rank superstitions and magic basis, so popular in medieval medicine. Altogether ophthalmology was greatly advanced in the Arab empire and it took Western medicine a long time, up to long after 1800, to catch up with it.

The Middle Ages in Europe

Ophthalmology in Europe during the Middle Ages is a sad and discouraging chapter. Let us first look at the record of the scholars, the learned physicians.

Constantinus Africanus (1015-1087), a converted Mohammedan from Carthage, became a monk at Monte Cassino and published a "Liber de oculis," which has been found to be a translation from an Arabic translation of Galen by Honein. Likewise, an old manuscript of Magister David Armenicus, "Compilatio in libros ad oculorum curationibus Accanomosali," (see above) is a translation from obscure Arab sources.

The lay medical schools of Salerno and of Montpellier did not contribute anything to ophthalmology. The references to the eye in their textbooks testify to the lack of practical experience by the authors.

Among the clerical students of medicine we find two popes: The Abbott Gerbert, a student of medicine, founded in 972 a medical school in Rheims and directed it for ten years. Even now we envy him the possession of a Latin translation of the best Greek ophthalmological author, Demosthenes of Marseilles, now completely lost. He was later elected pope and assumed the name Sylvester II (993-1003). He writes that he learned theoretical medicine but that he avoided (sic!) its practical performance.

Petrus Hispanus, son of a physician in Lisbon and medically educated, eventually became archbishop and was elected Pope under the name John XXI (†1277). He is the only contemporary pope whom Dante meets in his paradise. He wrote a "Liber De Oculis," which consists for the greater part of extracts and copies from Constantinus Africanus and Zacharias. Michelangelo Buonarotti copied some of Petrus' recipes for his own use (1564).

Master Zacharias studied ophthalmology with Theophilus, the personal physician of the Byzantine Emperor in Constantinople. His "Tractatus de passionibus oculorum qui vocatur Sisilacera" (from Sir-Al-Asrar, correct Arabic for secret of secrets) is most mediocre. We shall mention him below in connection with the shameless advice he offers the practitioner.

Arnaldus de Villanova, a Spaniard, worked in Montpellier. The "Libellum regiminis de confortatione visus," written on order of Pope Clemens V in 1308, is a plagiarism of the apocryphal Mesue the Younger. Other treatises, by Johannes de Casso (1346) and Barnabas di Reggio (1340), are likewise of little merit.

Guillaume de Salicet (ca. 1275) is one of the best authors of books on surgery during this period. He describes operations on the eye in detail and emphasizes the need of prolonged observation of an expert master *"quia haec non possunt per scripturam manifestari nec comprehendi per discipulum nisi viderit operari."**

We do not know who Salicet's teacher was. According to Hirschberg, one of the highlights of eye surgery in the late Middle Ages is the chapter on the eye in Guy de Chaulniac's (1298-1368) treatise on surgery (1365). The author was a cleric, temporarily in the services of the pope, which gave him the best access to existing literature.

* ". . . because these [sc. observations] can not be disclosed or understood by the pupil from mere description, but he must witness the operation."

He writes in Latin and combines good judgment, veracity, wide experience, and knowledge of the literature.

The Jews always had an excellent renown in ophthalmology. Many of them had crossed the border into Arab Spain for their studies. We have several codices containing collections of oculistic authors, Arab and Western, which were inherited in Jewish oculist families from father to son.

One of the earliest and most famous practitioners of ophthalmology in Europe was Benevenutus Grapheus of Jerusalem, in the 12th century. He knew Arabic and Arab ophthalmology. He was a converted Jew, Grapheus being the latinization of Hebrew ha-Rafee, the physician. In subsequent centuries he was widely cited on cataract and foreign bodies. There exist more than two dozen codices of his "Practica oculorum," mostly in Latin but also in old French, Provençal, and English. His work was printed as early as 1474.

When Alphonse, Count of Toulouse (1220-71), had some severe complaints of the eye, he negotiated through a group of French Jews with Habrahym, a Jewish ophthalmologist from Aragon, who agreed to come *"ex terra saracenorum"* after he had received *"inter alias securitates. . . patentes literas de conductu,"* a safe-conduct for his unincumbered return. Nothing is known of the outcome of his intervention.

King John of Bohemia (first half of 14th century) suffered from his youth from debility of sight. He called an oculist from France, but when he did not get cured he had him sewn in a sack and thrown into the river. Subsequently, he called a *"paganus de Arabia,"* who disappointed the king as well as others who consulted him at court. He only avoided the fate of his colleague because he had come on a sworn safe-conduct. Neither the famous surgeon Guy de Chaulniac nor a Jewish physician from Montpellier were able to cure the king, and so he finally went, completely blind, to die in the battle of Crecy (1346).

We also hear of successful extractions of cataract. For example, King Juan II of Aragon, father of Fernando the Catholic, called the Rabbi of Lerida, Abi-Abor, who successfully operated on cataracts in both his eyes in 1468.

A few words about hospitals. Tradition has it that the tyrant Dionysus of Syracuse blinded prisoners by suddenly admitting them from their dark dungeon to sunlight. It is also reported that 300 French crusading knights, when ransomed by St. Louis IX, King of France, from the Saracenes after years of imprisonment, returned blind or with impaired vision. While in those cases and similar ones that have been reported the sudden exposure to sunlight and maltreatment and trauma during imprisonment may have contributed to the eye trouble, its basic cause could have been avitaminosis A and xerophthalmia with supervening infections. However that may be, King Louis founded in Paris for his knights an institution called the Quinze Vingt (15×20), which was originally a home for the blind but developed later into an eye hospital.

One may very well say that the relationship between patient and doctor was usually based on mutual distrust. As regards regulation of the fees, the Visigoths in Spain fixed the price of a cataract operation in their code of law of the Seventh century at 5 Solidi, if successful—a remnant of Roman times. Benevenutus accumulated with his *"pulvis benedictum" . . . "incredibilem pecuniam."* The eye doctor received for one operation *"plus pecuniae. . . quam alius in decem curis aliorum morborum."*†

Henry de Mondeville complains, *"Je n'ai jamais trouvé d'homme assez riche ou plutôt assez honnête, de quelque condition que ce soit, religieuse ou autre, pour pouvoir payer au chirurgien ce qu'il avait promis sans y être forcé."*‡

† "more money . . . than others with ten cures of other ailments."

‡ "I have never encountered a man rich enough or rather honest enough, of whatever profession, clerical or otherwise, who would have paid the surgeon the promised fee without being forced to do so."

Many of the practitioners certainly fleeced the rich, but even one of the most successful ones, Benevenutus, writes *"sed semper habeatis misericordiam pauperum ad hoc ut deus det vobis gratiam bene operandi."*§ In an epoch of general piety, the physician must have been motivated by this belief much more than by moral prescriptions; thus, we may hope that their skill or incompetence, as the case may be, in the treatment of the eye was equitably distributed between the rich and the poor.

The regular practitioner had numerous competitors. *"C'est aujourd'hui la coutume de tous les princes, prélates, et homme du vulgaire dans tout les pays d'occident de n'avoir confiance dans aucun médecin scientifique"*‖ (Mondeville). According to Mondeville, "kings, princes, prelates, canons, priests, monks, dukes, nobility, and burghers meddle without science in dangerous surgical cures, in particular in the diseases of the eyes; now, the last is dangerous, difficult, and deceptive to a point that one finds very rarely a surgeon sufficiently expert in this matter. . . . Barbers, fortune tellers, money lenders, swindlers, forgers, alchemists, courtisans, procurers, midwives, old women, converted Jews, Saracenes, and all those who have, as it were, foolishly spent their goods" dabble in eye cures. *"Viles feminae et presumptuosae hanc artem usurpaverunt,"* (Bruno, 1282).¶ This was the fault of the public, nobles and commoners alike, but even more so of the physicians who shunned surgery, particularly of the eye.

"Operationes noluerunt medici propter indecentiam exercere sed illas barbarorum in manibus reliquerunt,"# an aloofness previously illustrated in the case of Gerbert. We find most scientific surgeons teaching that the surgeon should completely disinterest himself of eye practice and leave it to migratory specialists (G. Jacobi, Montpellier, 1364). It is a trait of the medieval mind—which we are unable to grasp—that ignorance was not only bliss, but an object of masochistic pride. It was as undignified and indecent to practice surgery as it was sinful and heretical to understand Greek; Rabelais was expelled from his monastery because he owned and read Greek books.

Especially in the early middle ages, it was mostly the midwives and herbalists who treated the eyes—with mothers' milk, with herbs, and with licking. Both they and their competitors, the monks, used prayers, incantations, and talismans. During the 12th century various concilia of the church actually prohibited any cleric to perform surgery because the profession had sunk so low in public esteem.

This mixture of empiricism and magic was continued by all the classes of illiterates and border-line characters enumerated before, above all by the itinerant healers who moved from one county fair to another and escaped the deceived patient *"habitā pecuniā,"* i. e., after having had their money. Both the illiterate and the learned doctors often seem to have indulged in outright swindle and fraud. Master Zacharias actually wrote the following *"Hoc valet ad deceptionem faciendam ut videaris quasi ab oculis pannum aufferre; accipe semen centrumgalli et dimitte parum, postea auferas eum [!] quasi pannum." "Si vis sophisticare infirmum et stantes dicas, quod illud tale est vermis qui destruebat oculum patientis."** Maybe for this reason he called his treatise "Secret of Secrets."

Without excusing Master Zacharias, we are reminded that Razi in his "Capitulum

§ ". . . but have always compassion for the poor, so that God may grant you the favor of successfully operating."

‖ "It is nowadays the custom of all princes, prelates, and others in all lands of the occident not to have confidence in any scientific physician."

¶ "Vile and presumptuous women have usurped this art."

"The physicians refused to perform operations for reasons of decency and so left these in the hands of barbarians."

* "The following serves the deception that you appear to remove the pannus from the eye. Take seed of millet, conceal it, and then remove it as if it were the pannus." "If you wish to bamboozle the patient and the bystanders, you may say this is the worm which threatened to destroy the patient's eye."

de deceptoribus" describes similar fraudulent practices in Arab medicine.

We doubt that one can pigeonhole the practitioners of these ages into classes of scholars, of empiricists, and of charlatans; nor can their motivations be sharply differentiated.

Spectacles

The history of medieval ophthalmology would be incomplete without a few words about a most important invention of the middle ages—the spectacles. The *ocularii* of Classical times were not makers of spectacles, as has been erroneously suggested, but they specialized in the manufacture of colored eyes for statues of the deceased, of emperors, and deities. The introduction of eyeglasses has a much more clear-cut story than that of most other discoveries. The famous English cleric Roger Bacon (1214-1294) mentions the possibility of aiding the old with their feeble eyesight by the use of plain-convex magnifying glasses. (The later claim by some Belgian optician that Bacon actually invented the eyeglasses, and that he was besides of Wallonic origin, is of course spurious.) It is, however, of interest that Roger Bacon was imprisoned in Tuscany around 1270 in the course of some papal intrigue. Francesco Redi, the famous physiologist of the Accademia della Crusca, gives in a book (Naples 1687) a number of scientific memoirs, among them, on pages 116-124, a *"lettera intorno all 'invenzione degli occhiali."* He quotes the chronicle of the Convent of Santa Caterina in Pisa, begun by Fra Bartolommeo da San Concordio, who died in 1347, after 70 years' service as a Dominican friar. Fra Bartolommeo mentions for the year 1313 *"Frater Alexander de Spina, vir modestus et bonus, quaecumque vidit aut audivit facta, scivit et facere: ocularia ab aliquo primo facta et communicare nolente, ipse fecit et communicavit corde ylari et volente. Ingeniosus in corporalibus in domo Regis aeterni fecit suo igenio mansionem."*† Redi subsequently compares Alessandro de Spina with another famous Pisan, Galileo Galilei, who constructed—just on a rumor that a Fleming had invented *"quell'occhiale lungo"*—a telescope—without ever having seen one.

Redi also quotes a Florentine family chronicle of 1299. The writer says *"Mi truovo cosi gravoso di anni, che non arei valenza di leggiere e scrivere sanza vetri appellati oKiali, truovati novellamente per comoditae delli poveri veKi quando affiebolano del vedere."*‡ Finally, he quotes the sermons of Fra Giordano da Rivalto, who died in 1311, *"Non e ancora vent' anni, che si trovo l'arte di fare gli Occhiali, che fanno veder bene che e una delle migliori arti, e delle piu necessarie, che il mondo abbia."*§ This puts the invention definitely in the last 20 years of the 13th century.‖ He furthermore quotes Bernard de Gordon, Professor in Montpellier, who recommends in his "Lilium medicinae" a collyrium *"et est tantae virtutis quod decrepitum faceret legere literas minutas absque Ocularibus."*¶ Similarly, Guy de Chaulniac says that as a last resort eyeglasses must be used. Thomas de Sarepta, a Polish contemporary of Chaulniac, believes that *"consuetudo vi-*

† "Frater Alexander de Spina, a modest and good man, was able to construct everything, which he had seen constructed or about which he had heard; when eyeglasses were first made by someone who did not wish others to partake of his art, he built them himself and communicated it willingly and with a glad heart. Ingenious in physical things, he built to his genius a mansion in the palace of the Eternal King."

‡ "I find myself so heavy with years, that I would be unable to read or write without glasses called occhiali, recently invented for the comfort of the poor old ones, when their eye sight weakens."

§ "It is not yet 20 years that the art of building eyeglasses was invented, which makes one see well, one of the best and most necessary arts in the world."

‖ According to a reference which I have not been able to verify, the Middle-High German poet Misner, or Meisner, mentions ca. 1270 that people use eyeglasses for reading.

¶ ". . . and it is so effective that it permits an old man to read small letters without eyeglasses."

dendi per oculos vitreos vel lancerneos ingrossat aciem oculorum."#

The names *occhiali* in Italian, *anteojos* in Spanish, and *Augenglaeser* in German are self-explanatory. The French *lunette* alludes to their round shape, and *lorgnon* is derived from the German *lauern* (to spy). Finally, *bericles* in old French manuscripts refers to the use of beryl, a colorless, transparent semiprecious stone, imported from India, for the making of spectacles. From this word is also derived the German *Brille*. The concave eyeglasses for the near-sighted were introduced much later, about the 16th century.

"The habit of looking through eyeglasses spoils the acuity of sight."

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Histopathology of the Star-Figure of the Macular Area in Diabetic and Angiospastic Retinopathy

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A white star-figure in the macular area of the retina is a typical ophthalmoscopic finding in advanced chronic diabetic and angiospastic retinopathy. It is composed of sharply limited white glistening spots which may be confluent and usually are arranged in a radiating manner around the fovea. These "hard" spots of the star-figure are ophthalmoscopically distinctly different from the "soft," fluffy, "cotton-wool" spots.

The histopathology of the macular star-figures in the retinae of two patients will be demonstrated in this study. Consideration will be given to the cause and manner of the development, as well as to the nature and significance, of this particular ophthalmoscopic finding. The histology of the typical cotton-wool spots in the retinae of a third patient will be described for comparison.

The present knowledge of the histopathology of the macular star-figure is composed of the findings of a large number of investigators and is very adequately summarized in the textbooks of Duke-Elder,[1] Friedenwald,[2] and Elwyn.[3] Destruction of retinal neurons, accumulation of exudate, the appearance of great numbers of special fat-laden phagocytes, and deposition of hyalin presumably contribute to the development of the white deposits of the macular star. The radial arrangement and the especially loose structure of the outer fibrillar layer of the macular region (Henle's fibers) has been accepted as the reason for the spoke-like pattern and the central localization of most of these conglomerate deposits. A detailed histologic description of the process which results in the occurrence of a star-figure, however, is still lacking in the literature.

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Method of Histologic Examination

The eyes of three patients used in this study were removed at the postmortem examination and fixed in brom-formalin (solution of Cajal). One half of each eye was imbedded in paraffin, cut in serial sections, and stained with hematoxylin and eosin and the Hotchkiss-McManus-Schiff stain.[4] Flat sections of the isolated retina of the other half of each eye and of the separately isolated macular areas of the eyes with the macular star-figure were made on the freezing microtome. The silver-carbonate methods of del Rio Hortega were used to stain these sections (see Scharenberg and Zeman[5]). The latter techniques have proved to be very useful in demonstrating histologic details of the human retina under normal and pathologic conditions (Wolter,[6-14] Wolter and Liss[15]). The methods of del Rio Hortega were combined in some sections with the oil red O stain, which selectively stains all lipid material a bright red. All illustrations presented in this paper are unretouched photomicrographs.

Report of Cases and Histologic Description

CASE 1.—A 54-year-old male diabetic patient was admitted to the Wayne County General Hospital on Feb. 28, 1956, because of dry gangrene and cellulitis of the left foot. At the time of admission, the blood sugar was elevated to around 300 mg/100 cc. and the blood pressure was 126/80. In the hospital, the patient was treated with insulin, penicillin, and blood transfusions and surgically with a guillotine amputation of the left foot. The ophthalmoscopic examination of both eyes revealed advanced diabetic retinopathy with typical star-figures composed of "hard" white spots in the macular areas. There were also vascular changes, a few peripheral, "soft," fluffy, so-called cotton-wool patches, and hemorrhages. Some of the hemorrhages were large and of an irregular shape, while others represented typical punctate hemorrhages and/or microaneurysms. The patient died suddenly on April 14, 1956, of pulmonary embolism.

The pathologic examination of the retinae of this first patient revealed diffuse advanced degeneration of the nervous elements of all layers (Fig. 1 *A* and *B*), proliferation, and scarification of the neuroglia. The blood vessels were fibrotic and markedly hyalinized. There were numerous typical capillary microaneurysms. Most of these microaneurysms presented complete obliteration of their lumens and represented solid formations comprised of hypertrophic endothelial cells, circularly arranged connective tissue fibers, and hyalin (Fig. 2). Some microaneurysms, however, still had lumens and were filled with blood. There were large irregular hemorrhages in different layers of the retinae and also typical punctate hemorrhages. The later represented cyst-like formations with walls of glial fibers, filled with blood exhibiting different stages of resorption. There were also here and there patches of degenerated and interrupted nerve fibers in the nerve fiber layer, with bizarre swellings of the distal stumps of the interrupted fibers. These latter patches were considered to be the histologic equivalent of the "cotton-wool" patches mentioned above in the clinical description (compare with the description of pathological findings in Case 3).

The central retinae of the eyes of the first case, which contained the star-figures,

Fig. 1.—*A*, degenerating ganglion cells (arrows) of the ganglion-cell layer of the first case, with diabetic retinopathy. *B*, advanced degeneration of a ganglion cell (arrow) and nerve fibers of the nerve fiber layer of the retina of the first case. Horizontal sections; Hortega method; photomicrograph; magnification × 700.

Fig. 2.—Obliterated capillary microaneurysm (*a-a*) with fat-filled phagocytes (gitter cells) (*b*) piled up around it. Horizontal section through inner nuclear layer of the retina of the first case, with diabetic retinopathy. Hortega method; photomicrograph; magnification × 600.

were cut, stained and examined separately. The histologic findings in these central retinal areas were so similar to those found in the second case that it seems reasonable to discuss later in this paper the changes of both cases together.

CASE 2.—A 68-year-old man entered the University of Michigan Hospital in coma with Cheyne-Stokes respiration on April 10, 1956. His blood pressure on admission was 220/148. The N. P. N. was 53 mg/100 cc. The ophthalmoscopic examination revealed the disk to be hazy in outline, with edema along the temporal border and gliotic changes on and around the disk. The retina vessels were narrowed and irregular in caliber. There was marked A-V notching. Numerous old "hard" white spots formed an extensive star-figure in the macular area. There were some hemorrhages. The ophthalmoscopic impression was that of Grade III angiospastic retinopathy bilaterally. The patient died on April 13, 1956, of myocardial infarction.

The histologic examination of the retinae of the eyes of this second patient with angiospastic retinopathy revealed advanced pathological changes. The retinae were swollen and contained extensive serous exudations, especially in an area around the optic disk. There was scattered neuronal damage throughout the retinae and some gliosis. The blood vessels were fibrotic and showed hyalinization. The hemorrhages in these retinae were found to be relatively small and irregular in shape and were scattered over the inner layers of the retinae. There were also areas of the nerve fiber layer which showed spot-like degeneration and swelling of the nerve fibers.

The posterior polar areas of the retinae of all four eyes of these two patients which contained the star-figures were examined separately. The pathology of these areas was generally the same in all four eyes and is described below.

There was very severe neuronal damage in the central parts of the retinae. The outstanding histologic finding, however, was the accumulation of great numbers of peculiar large round cells with a small nucleus. These cells undoubtedly were phagocytes, and their cell bodies contained large masses of phagocytized lipids. It was possible to demonstrate these lipids in a bright-red color with the oil red O. These masses were completely washed out, however, and the cell bodies appeared as empty vacuoles when the sections were treated with alcohol (Figs. 2 to 9). There were some degenerative changes in the pigment epithelium without proliferation and accumulation of lipids.

The fat-filled phagocytes were seen in all layers of the central retina. Large accumulations of them, however, were found in the outer fibrillar layer (layer of Henle's fibers) and in the inner nuclear layer of paracentral retina. In the center of such conglomerations of phagocytes there often was a capillary. In the case of diabetic retinopathy, this capillary usually was obliterated (Fig. 2), but such occlusion could not be seen histologically in the case with angiospastic retinopathy.

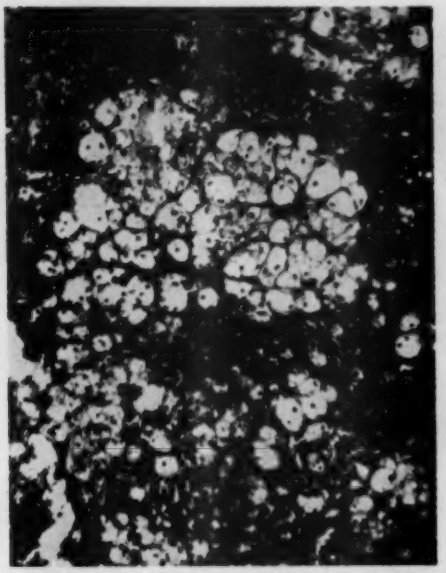


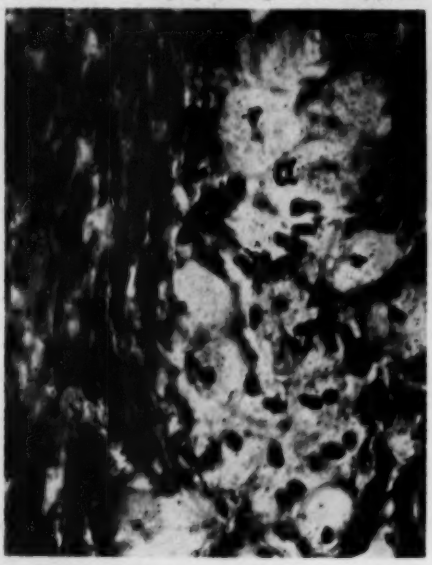
Fig. 3.—Low-power view of a horizontal section through inner nuclear layer of central retina of the first case, with diabetic retinopathy. There is a large accumulation of phagocytes (gitter cells). The cell bodies of the gitter cells appear as empty vacuoles, since the lipids have been washed out by alcohol. Hortega method; photomicrograph; magnification × 300.

Some of the groups of phagocytes and single phagocytes in such groups showed degeneration and necrosis. All stages of this process could be observed in the retinae of both cases, and these are demonstrated in Figures 5 to 10. Figure 6 shows a small group of undamaged fat-filled phagocytes (*a*) in the ganglion-cell layer of the central retina of the second case. Figures 7 and 8 were taken from the central retina of the same case and demonstrate that a breakdown of some of these cells occured, that the nuclei and the cell membranes disappeared, and that the lipid substances remained free in the tissue. These lipid substances of broken-down phagocytes contained scattered islands of hyalin. The beginning of this process of hyalinization is visible in Figures 7 and 8 (*c*) (Case 2). Later stages of the progressive hyalinization of these lipids are shown in Figures 9 and 10 (Case 2). Undamaged phagocytes with intact nuclei and cell membranes are still visible within the large accumulation of hyalin in Figure 9. The homogeneous hyalin body in Henle's fiber layer in Figure 10 (Case 2) shows only lipid remnants of one single phagocyte (*a*).

In summarizing the histologic findings in the central retinae of the four eyes, it can be said that an accumulation of fat-filled phagocytes was the predominant pathological finding. These phagocytes showed in many areas different stages of degeneration, and the remaining cellular debris had become hyalinized in other areas. The end-result of this degenerative process was large homogeneous patches of hyalin, most of which were arranged in a spoke-like manner in the spaces of the layer of Henle's fibers (Figure 11). There was no visible proliferation of cells of the pigmented epithelium. The lipids which had been phagocytized by the macrophages originated from destroyed retinal neurons.

CASE 3.—A 66-year-old woman died on April 16, 1956, at the Wayne County Gen-

Fig. 4.—Fat-filled phagocytes (gitter cells) (*a*) in Henle's fiber layer of the central retina of the first case, with diabetic retinopathy. Hortega method; photomicrograph; magnification × 600.



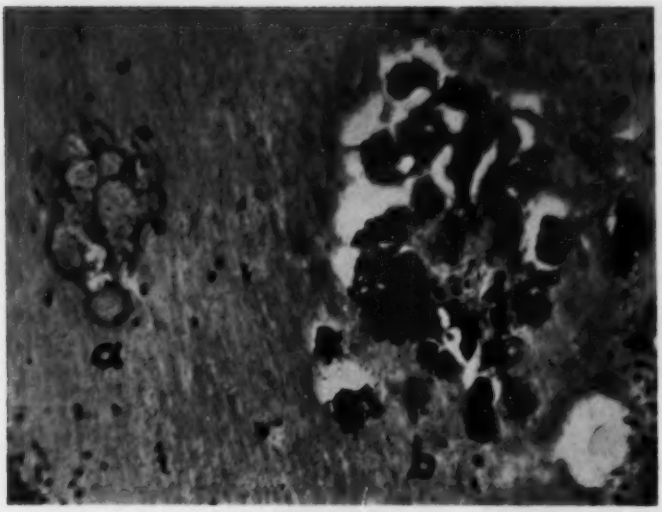


Fig. 5.—A group of fat-filled phagocytes (*a*) beside the hyalinized remnants of another group of phagocytes (*b*) in Henle's fiber layer of the retina of the first case, with diabetic retinopathy. The neurons are only very slightly stained in this section. Horizontal section; Hortega method; photomicrograph; magnification × 400.

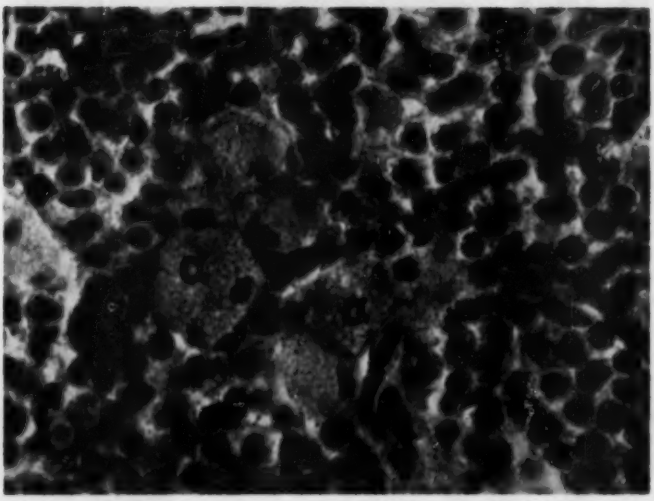


Fig. 6.—Small group of gitter cells (*a*) in the ganglion-cell layer of the central retina of the second case, with angiospastic retinopathy. Horizontal section; Hortega method; photomicrograph; magnification × 700.

eral Hospital a few days after her admission with an aspiration pneumonia associated with advanced diabetes mellitus. Her ophthalmoscopic examination at the time of admission revealed a chronic arteriosclerotic-diabetic retinopathy O. U. In this case, however, there were only many fluffy, "soft," "cotton-wool" patches and no "hard" glistening spots or a star-figure at the fundus. This patient also exhibited vascular changes, typical punctate hemorrhages, and microaneurysms.

Histologically all these clinical findings were confirmed; there were fibrosis of the blood vessels, hemorrhages, and microaneurysms. Advanced neuronal damage and gliosis was present throughout the retinae. In the retinae of this case, in the nerve fiber layer, there occurred many areas of a very special nerve fiber degeneration. There were no accumulations of phagocytes. In these degenerative spots of the nerve fiber layer, most of the nerve fibers were interrupted and the distal ends of each fiber

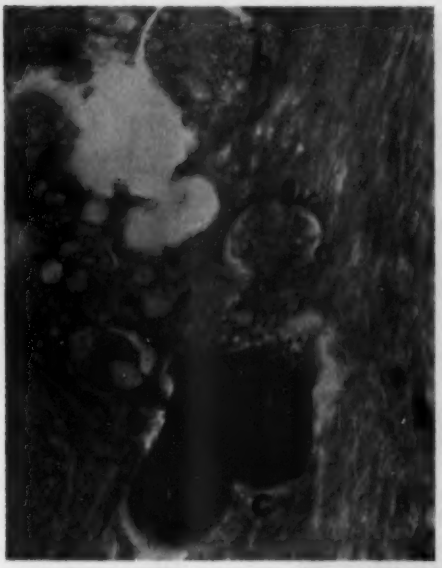
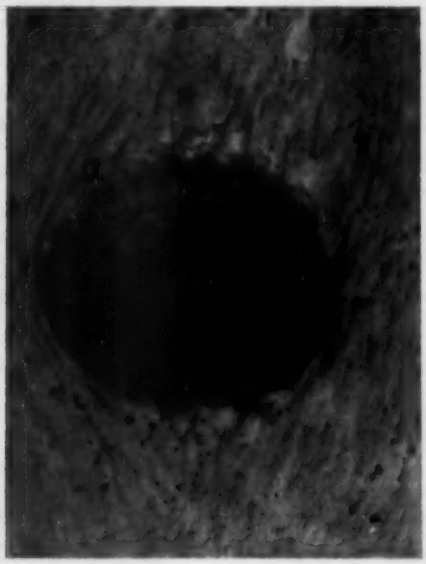


Fig. 7.—Degeneration (*a* and *b*) and hyalinization (*c*) of gitter cells in Henle's fiber layer of the second patient, with angiospastic retinopathy. Horizontal section; Hortega method; photomicrograph; magnification × 800.

Fig. 8.—Break-down (*a* and *b*) and hyalinization (*c*) of gitter cells in Henle's fiber layer of the retina of the second case, with angiospastic retinopathy. Horizontal section; Hortega method; photomicrograph; magnification × 800.

Fig. 9.—Advanced hyalinization of gitter cells in the layer of Henle's fibers in the retina of the second case, with angiospastic retinopathy. A few undamaged gitter cells are left within the hyalin (*a*). Horizontal section, Hortega method, photomicrograph, magnification × 800.

Fig. 10.—Final stage of hyalinization of debris of broken-down gitter cells (*a*) in Henle's fiber layer of second patient, with angiospastic retinopathy. Horizontal section; Hortega method; photomicrograph; magnification × 800.



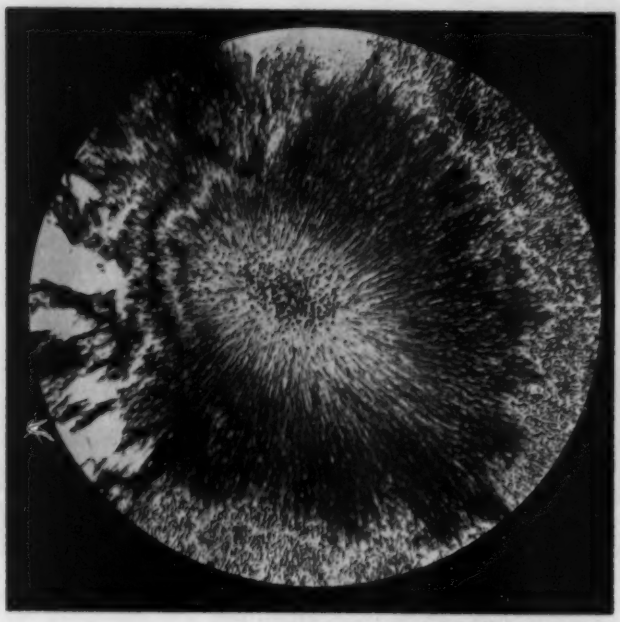


Fig. 11. — Horizontal section of central retina of a normal eye, which demonstrates the radial arrangement of Henle's fibers in the macular area. Hortega method; photomigrograph; magnification × 100.

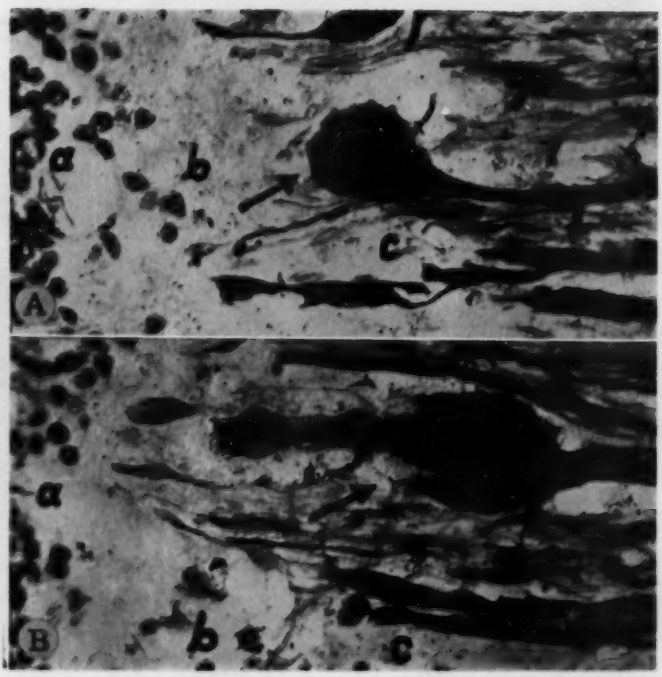


Fig. 12.—*A*, interruption of nerve fiber with formation of typical terminal swelling (arrow); *B*, beginning interruption of nerve fiber, dissolution of proximal part, and formation of end-bulb at the distal stump (arrow). Both sections from retina of the third patient, with diabetic retinopathy. (*a*) Inner nuclear layer; (*b*) ganglion-cell layer; (*c*) nerve fiber layer. Hortega method; photomicrographs; magnifications × 800.

Fig. 13.—Patch of terminal swellings of nerve fibers of the nerve fiber layer of the third patient, with diabetic retinopathy. All black-stained, round bodies represent end-bulbs of interrupted nerve fibers. Horizontal section; Hortega method; photomicrograph; magnification × 600.

presented a coarse, bulb-like swelling (Figs. 12 and 13). In and around these patches of degeneration, in the nerve fiber layer, it was possible to observe all stages of the development of such changes. Some of the nerve fibers were still continuous and only somewhat irregular in shape. The great majority, however, were interrupted, and there was dissolution of the proximal parts as well as the formation of large "terminal swellings" (Cajal [16]) at the distal ends of the degenerated nerve fibers. These terminal swellings of stumps of degenerated nerve fibers represented large round bodies which could be stained red with the oil red O stain. They were the elements of the patches of degeneration in the nerve fiber layer. The neuroglia, however, was not observed as participating in these formations. The great majority of the terminal swellings were directed towards the optic disk. A few of the ends with typical terminal swellings, however, pointed in an opposite direction (towards the periphery of the retina).*

* We believe that the fact of the occurrence of terminal swellings in both directions can be interpreted as further evidence for the existence of centrifugal nerve fibers in the nerve fiber layer of the human retina (see Wolter [14]).

Comment

The histologic findings, in the Cases 1 and 2, clearly indicate that accumulation of fat-laden phagocytes, with the subsequent secondary degeneration and hyalinization of the remaining debris, represents the histologic equivalent of the macular star-figures. Since all the spoke-like deposits in the layer of Henle's fibers were almost completely composed of hyalin and contained only few living phagocytes, it is reasonable to assume that these hyalin deposits must have been largely responsible for the ophthalmoscopic findings of the star-figures. The fact that these four retinae demonstrated all stages of the development of the hyalin deposits suggests that the degenerating phagocytes must be the origin of the deposits and that the latter cannot be considered as old, hyalinized exudate. There is little doubt that the lipids which were observed in the phagocytes represent the substance of broken-down neurons.

A most interesting question is that of the nature and origin of the phagocytes. The latter have been extensively observed and described in the retina and have been termed, variously, "bladder cells," "ghost cells," or "spectral cells" (Duke-Elder,[1] p.

2631). All investigators agree that these cells act as macrophages and phagocytize the substance of broken-down neurons. There is, however, no agreement as to the nature and origin of these macrophages. Most authors have believed that they are derived from the pigmentary epithelium (Krückmann [17]). Some have even suggested that the phagocytes may "metamorphose" under certain conditions into fibroblasts and thus finally take part in retinal scar formation. Others have considered them to be swollen and disintegrated leukocytes (Coats), degenerated rods and cones (Schweinitz and Shumway), or histiocytes (Marshall and Michaelson [18]). However, there was (and is) no agreement on these theories.

After consideration of the knowledge of modern neuropathology of the central nervous system there can be little doubt that the phagocytes of the retina, which are discussed here, are microglial elements. The retina, as well as the optic nerve of the eye, is a part of the central nervous system and is composed of neurons, neuroglia, vascular connective tissue, and microglia. The normal microglial elements of all parts of the central nervous system, including retina and optic nerve, are small cells with round nuclei and short branching processes. They were first described by del Rio Hortega [19] and are therefore known as "Hortega cells." These cells are of mesodermal origin and invade the nervous tissue in great numbers from the blood vessels under many pathologic conditions. The microglial cells are phagocytes which take up the debris of destroyed neurons (lipids). After phagocytosis, the microglial cells become large, round, fat-laden cells which are known under the name "gitter cells" (also sometimes granular compound corpuscles). The gitter cells are identical with the phagocytes here observed in the retinae of our first two patients.

It must be mentioned here that Marshall and Michaelson [18] considered the retinal phagocytes to be "histiocytes or macrophages arising from the reticuloendothelial system." We are in agreement with these authors, since the microglia represent the histiocytes of the central nervous system.

Friedenwald [2] has already pointed out that the development of the white deposits of the star-figure must be dependent upon primary changes of the small blood vessels. We here observed in the first case that the fat-laden microglial cells were piled up around obliterated capillaries (Fig. 2). In the second case it can be assumed that there were extensive vascular spasms of the small vessels. In many pathologic processes the microglia are known to carry the phagocytized cellular debris to the blood vessels. In our cases at least some of the small vessels were functionally destroyed. Therefore, the microglia could not deliver the lipids to the blood; they piled up in the retina, finally degenerated, and became hyalinized.

The third case exhibited fluffy, "soft" cotton-wool spots at the fundus only and had no "hard" patches of a star-figure. It is important to emphasize the histologic difference between the spots of the star-figure, which are described above, and the cotton-wool spots. The latter ophthalmoscopic finding was seen to be caused by a circumscribed, patch-like degeneration of nerves of the nerve fiber layer. In these patches the nerve fibers were interrupted, the proximal parts of the fibers had disappeared, and their distal stumps showed bizarre bulb-like terminal swellings. These terminal swellings are identical with the "varicose thickenings," "ganglioforme swellings," or "cytoid bodies" of earlier authors (Friedenwald,[2] Duke-Elder,[1] or Cone and Macmillan [20]). We believe that these latter names are misleading, since the terminal swellings are not at all a specific finding in the pathology of the retina. They are very well known from general neuropathology studies as a nonspecific pathologic reaction of nerve fibers throughout the peripheral and central nervous system (Ramon y Cajal [16]). In the present study,

the neuroglia has not been observed as participating in the formation of the cotton-wool patches.

Summary

A detailed description is given of the histopathology of typical examples of macular star-figures of the fundi in two patients with angiospastic and diabetic retinopathy. The histology of typical cotton-wool patches in a third patient, with diabetic retinopathy, is described for comparison.

Dr. Harold Falls, of the Department of Ophthalmology of the University of Michigan Hospital, gave advice and help in obtaining the eyes used in this study.

Neuropsychiatric Institute, University of Michigan.

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Temporal Aspects of the Human Electroretinogram

A Study of the Implicit Time-Amplitude Relationship of the B-Wave

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During the past decade intensive work by psychologists, physiologists, and ophthalmologists has shown that the human electroretinogram (ERG) is a result of two basic forms of response—scotopic and photopic. The differentiation of these two components has been achieved through the study of the ERG in normal, color-blind, and night-blind subjects, under different states of adaptation, with stimuli of varying wavelengths and intensities.

The scotopic and photopic components of the human ERG are similar in that each consists of a negative deflection succeeded by a positive one. There is a difference, however, in their temporal characteristics, the photopic response following a more rapid course than the scotopic response. Furthermore, the photopic positive wave (x-wave) maintains a constant latency and implicit time,* regardless of the experimental condi-regardless of the experimental conditions, tions, whereas the scotopic positive wave (b-wave) shows a marked variation.

It is the purpose of this investigation to study the relation between the implicit time and amplitude of the scotopic b-wave, while varying the wavelength and intensity of the light stimulus.

Methods

Preliminary experiments were done with six normal subjects. Since it was necessary to have a high signal-to-noise ratio, the three subjects with the highest response amplitude and the steadiest baseline were selected for more detailed studies. Recordings were also taken from a totally color-blind and a congenitally night-blind subject. Details of clinical, psychophysical, and ERG studies in these two subjects will be published in a subsequent paper.[1a]

The potentials were picked up from the anesthetized cornea of the left or right eye with a Burian-Allen contact lens electrode. The reference electrode was applied to the bridge of the nose, and the ground electrode was placed against the forehead, both fixed by means of a plastic holder.

The electrodes were connected to the input of a capacity-coupled preamplifier (Grass P 5) with a sufficiently high time constant.† The amplified potentials were led to one D. C. channel of a double-beam cathode ray oscilloscope (ETC Model K 26). The second channel was connected to a photocell for simultaneous registering of light stimuli. The recordings were made with a Grass Kymograph Camera (Model C4D) using the moving film operation (50 mm. per second), with the CRO sweep switched off.

The recording system was operated by a manual switch, which triggered the camera so that the shutter opened and the film moved for one second. By interposition of a Grass Electric Stimulator (Model S4B)

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* Implicit time refers to the interval from onset of light stimulus to peak of wave.

† The over-all frequency response, checked by a sine wave generator, was found to be constant for frequencies lower than 1 cps. The slowest waves in the present study were equivalent to a fundamental frequency of 4 to 5 cps. Therefore, the possibility of measurement errors due to frequency response of the amplifier system could be excluded.

between the relay output of the camera and the Photic Stimulator (Grass Model PS1), it was possible to deliver the light stimulus with a set delay. A fixed delay of 0.25 second was found satisfactory because it allowed recording of the baseline before and after the response.

The light stimulus produced by the Photic Stimulator was a flash with a fixed duration of about 10 microseconds and a peak luminance of about 6×10^{7} millilamberts (the luminance was calculated on the basis of figures supplied by the manufacturer). Owing to the extremely short duration of the stimulus, the subjective brightness was actually about 4 logarithmic units below this figure.

The Photic Stimulator was set into a blackened cylinder, the open end of which was equipped with a holder for filters. The distance between the subject's eye and filters was 12 cm., with 40 cm. between the subject's eye and the front glass of the Photic Stimulator. At this distance, the diameter of the stimulus patch was 18 degrees.

The intensity of the light stimulus was varied over a range of 4 logarithmic units by means of two sets of neutral filters (Inconel), with 50%, 25%, and 5% transmission. The spectral composition was varied with the use of color filters: standard Wratten filters Nos. 70 (deep red), 29 (red), 22 (orange) and a Grass blue filter. To confirm the absence of the rapid photopic component for the highest intensity blue and white stimuli used in the experiments, the flicker fusion frequency was determined.‡ It was found to lie consistently below 20 flashes per second, indicating that only the slow scotopic component was present.[1]

Following previous exposure to an average room illumination of about 8 foot-candles, the ERG recordings were begun after

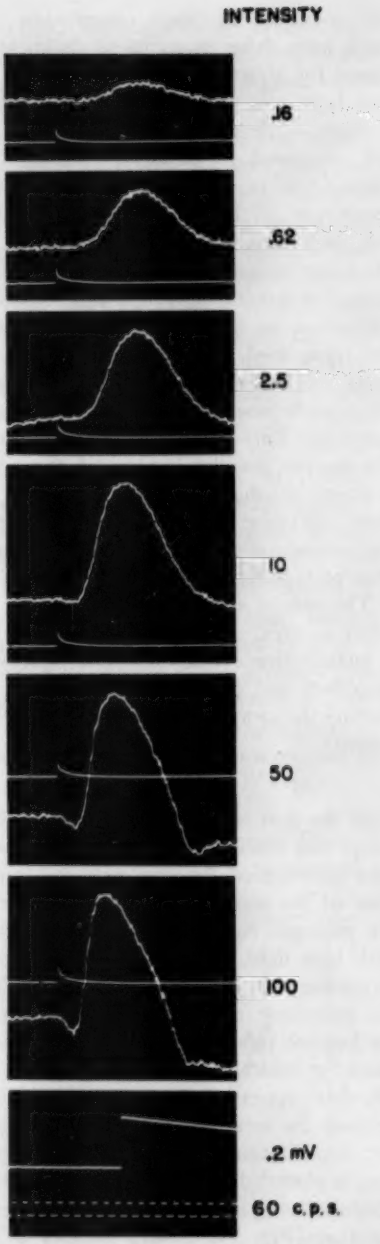

Fig. 1 (Subject 1).—The scotopic ERG with blue light stimuli of different intensities (arbitrary units).

‡ Dodt[1] has shown that the photopic ERG has a range of flicker fusion frequency from 25 to 70 flashes per second. Maximum scotopic fusion frequency is about 20 flashes per second, as demonstrated by this author in a totally color-blind subject.

30 minutes of dark adaptation. The tests were done in complete darkness and lasted for about one hour. A dim red fixation light was used in several experiments.

Since some of the results in this work are compared to those of Auerbach and Burian,[2] it is important to note that the same types of Photic Stimulator and Wratten color filters were employed in each case. However, by use of a double-channel oscilloscope for simultaneous recording of stimulus and response, instead of the single-channel recording used by Auerbach and Burian, a more exact measurement of the temporal relations between stimulus and response was possible. This fact is mentioned because the figures for the latency of the a- and x-waves in the present experiments, and those of other investigators, are about 10 milliseconds shorter than those reported by Auerbach and Burian.

The results are based on a total of 1004 ERG records, of which 736 were used for a quantitative evaluation. The figures for amplitude and/or implicit time in each subject are the mean values of 6 to 12 individual records.

Results

In the first series of experiments, an attempt was made to study the effect of stimulus intensity on the amplitude and implicit time of the scotopic b-wave. To eliminate the photopic component, testing was done with blue light. Figure 1 shows that with increasing stimulus intensity not only does the amplitude of the b-wave increase but the implicit time decreases. This is demonstrated graphically in Figure 2. In this Figure, there appears to be no linear correlation between the reciprocal changes in amplitude and implicit time. However, when implicit time is plotted directly against amplitude the resulting curve suggests a simple exponential function (Fig. 3). This possibility will be discussed in connection with Figure 6, in which the experimental data for all subjects and different wavelengths are evaluated.

In a second series of experiments, the investigation concerned the amplitude-implicit time relationship of the scotopic b-wave with white, orange, and red stimuli in addition to blue. With white light it was necessary to use stimuli of low intensity in order to avoid interference of photopic potentials with the scotopic b-wave, except in the case of a color-blind subject. With stimuli of longer wavelengths, the study was restricted to a range of stimulus intensities in which a separation of photopic and scotopic components was evident. Figure 4 demonstrates examples of the waves obtained with various light stimuli. The responses to blue light (4*A*) and to low-intensity white light (4*B*) are simple positive waves representing the scotopic b-wave. With red light the scotopic b-wave potential is preceded by the early photopic component

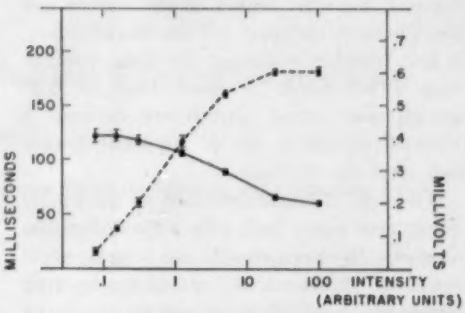

Fig. 2 (Subject 2).—Variation of amplitude (dotted line) and implicit time (continuous line) of the b-wave as function of stimulus intensity (blue light). Each point is the mean value of six responses. The vertical lines represent the standard deviation.

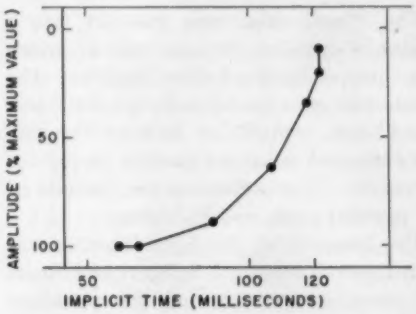

Fig. 3 (Subject 2).—Relation between amplitude (in per cent of the maximum value) and implicit time of the b-wave, with blue light stimuli. Plotted from the same data as Figure 2.

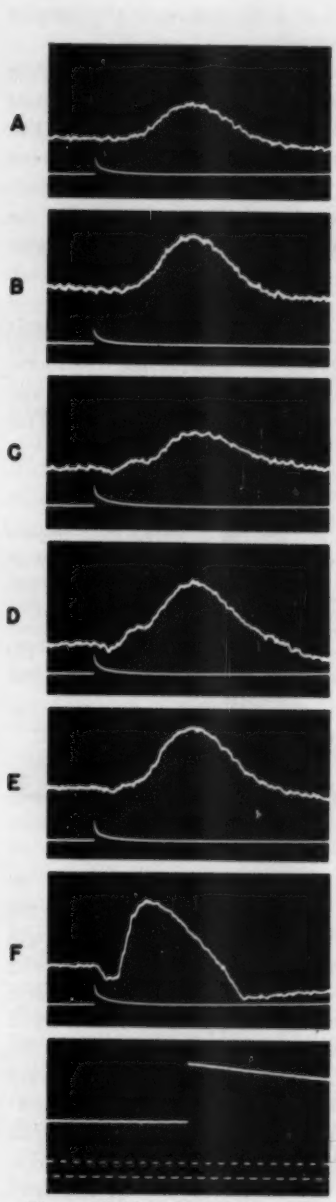

Fig. 4 (Subject 1).—Pattern of response in the ERG (dark adaptation) to stimuli of different colors. The isolated scotopic b-wave is present with blue light and with a white light stimulus of low intensity (*A*, *B*). It is preceded by the photopic x-wave with stimuli of longer wavelengths (*C*, *D*, *E*, *F*). (Stimulus intensity in Figure 4 *F* is 80 times that of Figure 4 *E*, and is recorded with the amplification reduced by a factor of 0.48).

(4*C* and *D*). In the case of orange light this separation of both components is less distinct, particularly with the high-intensity stimulus (4*E* and *F*).

The values for the amplitude and implicit time of the b-wave obtained with blue, red, orange, and white stimuli (Fig. 5) were plotted in the same manner as in the first experiment, where only blue stimuli were used (Fig. 1). The points plotted for the white and long wavelength stimuli were in close agreement with those of the blue curve in demonstrating the relation between amplitude and implicit time. The implicit time showed a limited range from a maximum of 120-140 milliseconds to a minimum of 60-70 milliseconds. A similar range (60-130 milliseconds) was obtained for the scotopic b-wave in a totally color-blind subject. In this case it was possible to use white light stimuli of high intensity, since the color-blind subject lacks an x-wave[8] (as evidenced here by a maximum ERG flicker fusion frequency of less than 23 per second). Therefore, it is apparent that shortening of the implicit time is an inherent property of the b-wave and is not caused by the appearance of a photopic x-wave.

The curves obtained in Figures 3 and 5 suggest a definite correlation between the

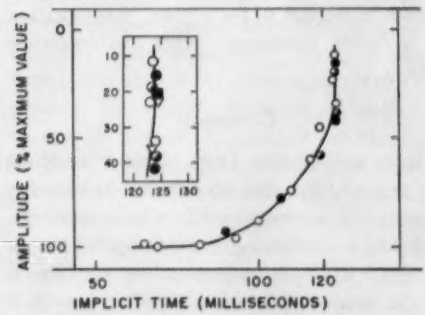

Fig. 5 (Subject 1).—Relation between amplitude (in per cent of maximum value) and implicit time of the b-wave with blue (open circle), white (triangle), orange (black circle), red (black and white circle), and deep red (black square) light stimuli of different intensities. The insert illustrates the upper portion of this curve in greater detail. Each point is the mean value of nine responses.

amplitude and the implicit time of the scotopic component, regardless of the wavelength producing it. In order to formulate this relation between amplitude (a) and implicit time (t) in mathematical terms, a simple exponential equation is proposed of the general type

$$y=y_0e^{-kx} \quad (1)$$

Since the amplitude varies from zero to a maximum value (A_{max}) and the implicit time has both a minimum (T_{min}) and a maximum value (T_{max}), this equation may be expressed as follows:

$$t=T_{max}-(T_{max}-T_{min})e^{-k(1-a/A_{max})} \quad (2)$$

To test the application of this formula, data were compiled for three experimental subjects with stimuli of different wavelengths and intensities (Fig. 6). The mean values for T_{min}, T_{max}, and A_{max} were calculated and substituted in the equation. As shown in Figure 6, for $k=4.6$, this equation is in close agreement with the empirical data.

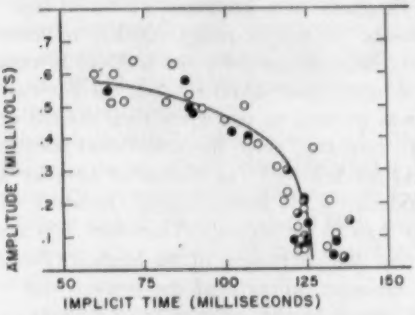

Fig. 6.—Relation between amplitude and implicit time of the b-wave with blue (open circle), orange (black circle), and red (black and white circle) light stimuli of different intensities. Collected data of three different subjects. Each point is the mean value of 6 to 12 responses in the same subject. The smooth curve represents the theoretical equation (see text).

Comment

It is well known from pioneer work on the animal ERG that an increase in stimulus intensity is accompanied by a gain in amplitude and a shortening of the temporal course of the ERG.[4] A corresponding shortening of the implicit time of the complex positive wave in the human has been observed by several investigators, using white light stimuli.[5-7] These experiments, however, did not explain whether this shortening was attributable solely to the b-wave or whether it was caused by the increasing participation of the rapid photopic x-wave in the complex positive response.

On increasing the wavelength of the light stimulus, Monnier[5] observed a shortening of the implicit time. He suggested that this phenomenon may result from the appearance of the rapid photopic component, corresponding to the higher sensitivity of the photopic system to light of longer wavelengths. In this experiment, Monnier adjusted the light intensity so that different colors elicited responses of equal amplitude. However, under his experimental conditions, no temporal separation of the scotopic and photopic components was attained. This makes it difficult to draw conclusions regarding the scotopic b-wave from Monnier's work.

Schubert and Bornschein[8] studied the ERG with a progressive shortening of the spectrum starting at the short wavelength end. Under these conditions, an increasing temporal separation of the x- and b-waves was observed. This separation resulted from an increase of the implicit time of the b-wave, while the implicit time of the x-wave remained constant. It was not clear, however, whether the increase in implicit time of the b-wave was a specific effect of color, or whether it was an intensity effect related to the low effectivity of the long wavelengths for the scotopic system.

From the previous studies, it was apparent that there were two major difficulties which had to be met in studying the implicit time of the b-wave. In the first place, it was

necessary to prevent the encroachment of the x-wave on the b-wave. This was done by excluding the x-wave with the use of blue light, or white light of low intensity, and/or by separating the x-wave from the b-wave with red light. Secondly, it was necessary to avoid the problem which this use of colored stimuli created, namely, the need for equating intensities in terms of the spectral sensitivity of the responding system. This was done by plotting the implicit time of the b-wave directly as a function of the amplitude of the response to different stimuli rather than as a function of the stimulus intensity or wavelength themselves.

The results of these experiments reveal that the implicit time of the b-wave varies between 60 and 140 milliseconds as a simple exponential function of the amplitude. This function was not influenced by changes in the spectral composition of the stimuli. It may be concluded that the influence of colored light stimuli on the implicit time of the b-wave is related to intensity, and not to a specific effect of wavelength.

In a recent study of the photopic-scotopic relationships in the human ERG, Auerbach and Burian [2] investigated the effect of dark adaptation on the response to red and orange lights. They concluded that the late positive deflection following the x-wave, after stimulation with red light, which was interpreted by Adrian,[9] Armington,[10,11] and Schubert and Bornschein [8] as a scotopic b-wave, is actually a photopic red response. They based this conclusion on the fact that this "late positivity" could be elicited with red filters (Wratten 70 and/or 29) but not with orange filters (Wratten 22), and that the long implicit time of this wave (120-140 milliseconds) was incompatible with their conception of the properties of the b-wave. However, these authors did not take into account the influence of the intensity of light stimulus on the implicit time. As shown in Figure 4, this "late positivity" can be produced in a normal subject not only by red light but also by orange, white, and blue light, if the intensity of the light stimulus is sufficiently

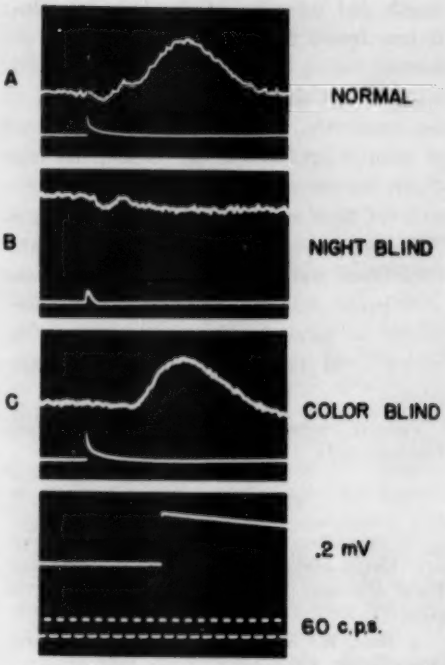

Fig. 7.—Patterns of response in the ERG (dark adaptation) to red light stimuli (Wratten 29) in normal (*A*), night-blind (*B*), and color-blind (*C*) subjects. The night-blind subject lacks the scotopic b-wave ("late positivity"), whereas it is present in the color-blind subject. The only positive response in the night-blind is the photopic x-wave, which is absent in the color-blind.

low. This proves that this wave cannot be a specific red response. Furthermore, as Auerbach and Burian have already pointed out, the "late positivity" develops slowly during the course of dark adaptation, suggesting a scotopic function. Finally, as shown in Figure 7, absence of the "late positivity" in a night-blind subject, and its presence in a color-blind subject, following stimulation with red light, clearly demonstrates the scotopic nature of this wave. There can be no doubt, therefore, that the "late positivity" is not a photopic red response but is simply the scotopic b-wave.

Summary

The relationship between the implicit time and amplitude of the human scotopic b-wave has been studied while varying the wave-

length and intensity of the light stimulus. It was found that the implicit time of the b-wave varies between 60 and 140 milliseconds as a simple exponential function of the amplitude. Furthermore, the influence of colored light stimuli on the implicit time of the b-wave is related to stimulus intensity and not to a specific effect of wavelength.

The results obtained from normal, totally color-blind, and congenitally night blind subjects prove that the "late positivity" interpreted by some investigators as a specific photopic red response is actually the scotopic b-wave.

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An Explanation of Haidinger's Brushes

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The human eye is a most efficient instrument for detecting light and analyzing certain of its properties. Differences of intensity and of wavelength and the spatial distribution of primary or secondary sources of light are perceived with great precision, but one important quality of light, its plane of vibration, is perceptible only with difficulty and under especially favorable circumstances.

We have reasons to believe (von Frisch [1]) that in this respect the eyes of bees are superior to the human eye.

The first to observe that the polarization of light is visible without auxiliary means was the mineralogist W. von Haidinger [2] (1844). He described as *Lichtpolarisationsbüschel* the phenomenon which was later to become known as Haidinger's brushes.

Haidinger's brushes are best seen by looking through a polarizer at the clouded sky or some other uniform white surface. The phenomenon vanishes by local adaptation after a few seconds of observation. It is easier to observe if the polarizer is slowly rotated or if the observer alternately looks through two polarizers oriented at right angles to each other.

A complete description of Haidinger's brushes was given by Helmholtz,[3] who also reproduced a colored drawing. The phenomenon consists of two yellow sheaves radiating in opposite directions from the point of fixation. The sheaves are flanked by blue hyperbolic regions. The axis of the hyperbola corresponds to the plane of vibration of the electric vector of linearly polarized light, or, in the case of elliptically polarized light, to the major axis of the ellipse.

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The contradictory statements of Helmholtz and Tschermak [4,5] on the orientation of Haidinger's brushes are caused by their use of the ambiguous term plane of polarization. Before polarization was well understood, light reflected from a dielectric at the polarizing angle was said to be polarized in the plane of incidence. Now it is known that the electric vector is at right angles to the plane of incidence. The plane of polarization of Helmholtz is therefore perpendicular to the plane of vibration. Tschermak's [4] discussion of an experiment with a crystal of tourmaline (p. 105) shows that he uses the term plane of polarization in a different sense. To him it signifies the plane of vibration.

According to Helmholtz, Haidinger's brushes are due to the presence of a radial analyzer in the macula lutea. In this part of the retina Müller's (neuroglial) fibers are radially arranged. Each fiber is supposed to be dichroic like a crystal of tourmaline or herapathite (quinine iodosulfate). A dichroic crystal is double-refracting and also absorbs one of the polarized refracted rays more than the other. The theory of the radial analyzer seems to have been almost universally accepted, but certain modifications have been proposed.

A number of authors take the analyzing action to be due to Henle's fibers (the nerve fibers) instead of Müller's. This is the opinion most commonly found in the standard textbooks (Duke-Elder,[6] Viallefont [7]).

A hypothesis originated by Gullstrand, that the site of the radial analyzer is in the retinal receptors themselves, will be discussed below.

The theory of the radial analyzer explains the shape of Haidinger's brushes, but not their colors. It is tempting to suppose that

the colors are in some way connected with the yellow pigment of the macula. Helmholtz supposed that the yellow pigment was dichroic and a part of the radial analyzer. If the absorption of blue light is greater in the extraordinary ray than in the ordinary, the colors of Haidinger's brushes are adequately explained. A number of authors have proposed a simplified version of Helmholtz' explanation. The yellow pigment is not dichroic but acts as an ordinary yellow filter. The yellow sheaves of Haidinger's brushes are explained in this way, and the blue hyperbolic regions are supposed to be due to contrast. This explanation is not satisfactory. The intensity of the blue color is greater than would be expected from a phenomenon of contrast, and the blue color is not more marked at its border with the yellow. Furthermore, the afterimage of the blue hyperbolic regions is even more distinct than that of the yellow sheaves, a fact not easily reconcilable with the supposition that the blue color is due to contrast.

To Helmholtz' original version several objections may be made:

1. It is doubtful whether the yellow pigment of the macula is present during life. I do not intend to discuss this most controversial matter here. A short summary of the question is given by Hartridge,[8] and a more detailed discussion, by Nordenson.[9]

2. The yellow pigment is not associated with Müller's or Henle's fibers. Polyak [10] has shown that it permeates diffusely all structures inward from Layer 4. It seems therefore improbable that it can be a part of the radial analyzer in the manner suggested by Helmholtz.

3. In the foveola the yellow pigment is practically absent (Polyak [10]), but the central part of Haidinger's brushes is not blue but yellow to most observers. However, Holm [11] (p. 28) has observed that the center of the brushes is blue to a minority of subjects.

It would appear, then, that the yellow pigment of the macula cannot adequately explain the colors of Haidinger's brushes.

Gullstrand [12] found that when using a stenopeic hole he could not obtain parallax between the peripheral part of Haidinger's brushes and the entoptic macula. Between the brushes and the entoptic fovea he saw a distinct parallax. As the entoptic fovea is due to the most superficial layers of the retina and the entoptic macula to the deepest layers, Gullstrand concluded that the site of the analyzer must be in the retinal receptors. The dichroism of the receptors was supposed to be due to subtotal reflection occurring in those rays falling obliquely on the receptors. If the light is polarized, the loss by subtotal reflection will be different in different meridians. If the receptors are dichroic to blue light but not to longer wave-lengths, the colors are explained.

Stanworth and Naylor [13] have proposed a modification of Gullstrand's explanation. They suppose that only the blue receptors are dichroic and that the dichroism is due to a regular arrangement of the molecules of the blue substance. The hypothesis of Stanworth and Naylor explains the shape and colors of Haidinger's brushes equally as well as that of Gullstrand. It is based on an observation of Schmidt [14] that the rods are dichroic. These authors believe with Willmer [15] that the blue receptors are rods or something intermediate between rods and cones. If the hypothesis of Willmer is correct, it seems reasonable to suppose that the blue receptors are dichroic and not those of other colors. But the rods are not dichroic for light passing along their axes. Stanworth and Naylor suppose that the light passes obliquely with several internal reflections through the outer part of the receptor and that the postulated dichroic action could take effect during this passage.

There is one objection that is common to the hypothesis of Gullstrand and to that of Stanworth and Naylor. If light falls normally on the retina, the dichroic action of the receptors according to both theories will be small, but if it falls obliquely the number of internal reflections in the outer member of the receptor will be multiplied and the

dichroic action much increased. But Haidinger's brushes are equally well seen by rays that have passed through all parts of the pupil. Hartridge [8] (p. 334) observes that they are not more evident when using peripheral rays only or when using central rays only. It is easy to verify the observation of Hartridge using a stenopeic hole of 2 mm. diameter and with the pupil dilated with homatropine. Bárány's [16] investigation of the Stiles-Crawford effect in polarized light confirms the evidence of Hartridge's experiment.

A further objection to the explanation of Stanworth and Naylor was made by Sloan and Naquin,[17] who observed that Haidinger's brushes were visible to a subject with tritanopia.

If white polarized light passes through a retarding plate or a piece of birefringent material and then through an analyzer, the emerging light will be colored. On rotation of the analyzer the color will change, and it is possible to show that the colors are complementary if the analyzer is rotated 90 degrees. The colors are due to interference, and a change of the thickness of the retarding plate will cause a change in the colors.

As the colors of Haidinger's brushes, blue and yellow, are complementary, and the angle between the axis of the yellow sheaves and that of the blue hyperbola is 90 degrees, it seems possible that the interference of polarized light might be the cause of the phenomenon.

Such explanations have been attempted by Silbermann,[18] Brewster,[19] and Cogan.[20] These attempts have not been successful, and the interference theory of Haidinger's brushes has not been generally accepted. The aim of the present investigation is to construct a model of Haidinger's brushes based on the interference theory. A comparison between the model and the brushes will facilitate the discussion of the theory.

Most investigators have regarded Haidinger's brushes as a simple optical phenomenon. If this is true it should be possible to reproduce it by an optical arrangement.

Tschermak-Seysenegg [4] has constructed a radial analyzer, or *Radiärnicol*. This is made from a rectangular piece of Polaroid with the optic axis parallel to one of the sides of the rectangle. From this are cut out (as shown in Fig. 1) 12 isosceles triangles with

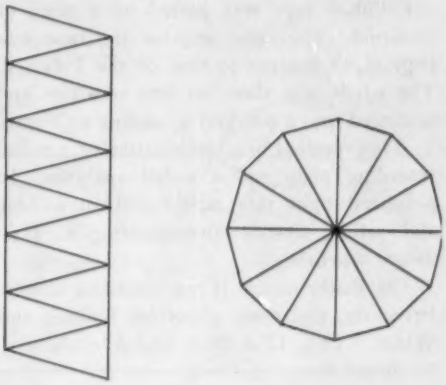

Figure 1

their bases parallel to the long side of the rectangle and with their top angles 30 degrees. These triangles are then arranged in a regular dodecagon. A better approximation of a radial analyzer can be made from 16 or 24 triangles, but this simple model is satisfactory for purposes of demonstration.

If the radial analyzer is combined with a polarizer, dark and light sectors are seen. When a yellow filter is added to the combination, we have a model of the simplified version of Helmholtz' hypothesis. The yellow sectors correspond to the sheaves of Haidinger's brushes and the dark sectors to the blue regions, the color of which according to this explanation is due to contrast.

If, instead of the yellow filter, a piece of birefringent material is inserted between the polarizer and the radial analyzer, and rotated to a suitable position, the sectors will be colored in complementary colors.

In my attempts to construct an adequate model of Haidinger's brushes I have used cellophane as the birefringent material. Three different kinds of cellophane are available commercially. The thickest meas-

ures 40μ and weighs 60 gm/sq. meter. Its optic axis is parallel to the fine striation of the material. To a greenish-yellow monochromatic light the phase-difference measured with primitive methods is about 180 degrees. The cellulose tape available to me is made from this kind of cellophane.

Cellulose tape was pasted on a piece of Polaroid. The optic axis of the tape was kept at 45 degrees to that of the Polaroid. The whole was then cut into triangles and arranged into a polygon according to Figure 1. This resulted in a combination of a radial retarding plate and a radial analyzer. In polarized light this model will show blue and yellow sectors corresponding to Haidinger's brushes.

The mathematics of the model is simple. From the equations given by Jenkins and White[21] (Eq. 12 d, 26 d, and 26 e), it may be shown that

$$\frac{R^2}{A^2} = \frac{1}{2}\,(1 \pm \cos\delta \times \cos 2\phi) \qquad (1)$$

where

A^2=the intensity of the original linearly polarized light

R^2=the intensity of the light of wavelength λ that passes the radial analyzer at a meridian of ϕ degrees with the original plane of vibration

δ=the phase difference of the retarding plate for light of wavelength λ.

The positive sign of the equation should be used if the radial analyzer is made with the optic axis of the Polaroid radial; the negative sign, if it is at right angles to the radii. If the phase difference for light of wavelength λ' is known to be δ it is possible to calculate δ for wavelength λ (Jenkins and White,[21] Eq. 26 b).

$$\frac{\lambda'}{\lambda}\,\delta' \qquad (2)$$

To get a clear picture of the distribution of colors it is necessary to calculate the intensities of four different wavelengths for six different values of ϕ.

With the present model, if the optic axis of the Polaroid is radial the blue sectors are always parallel to the plane of vibration of linearly polarized light. If the plane of vibration is rotated this causes a rotation of the sectors in the same direction and to an equal degree. The colors of the sectors are not influenced by rotation. This applies equally well to Haidinger's brushes.

With the model the midlines of the blue and yellow sectors present the deepest color, which fades away at the boundary between two sectors. In this respect the model differs from Haidinger's brushes. At this boundary, however, simultaneous contrast would be expected to reinforce the color on either side and might well produce the uniform blue and yellow colors of Haidinger's brushes.

Stokes[22] investigated the visibility of Haidinger's brushes in monochromatic light of different wavelengths. He found that the brushes were invisible if the wavelength exceeded 5270 A. (line E of Fraunhofer). This does not apply to the present model, but it seems possible to satisfy the condition reasonably well by a suitable choice of the thickness of the radial retarding plate. If the value of δ for light of wavelength 6000 A. is 90 degrees and the radial analyzer is made with the optic axis of the Polaroid at right angles to the radii, the values of R^2/A^2 calculated by equations (1) and (2) are shown in Figure 2.

The diagram shows that for yellow light the intensity is equal in all meridians. For blue and green light the differences are much greater than for red light. With a radial analyzer made of Polaroid the differences would be visible also in red light, but the radial analyzer of the eye is probably less efficient.

According to the interference theory, the colors of Haidinger's brushes are determined by the thickness of the radial retarding plate. A model was made according to the description given above but with double layers of cellulose tape. With this model the sectors were red and green instead of blue and yellow. As Haidinger's brushes are seen by all observers in about the same colors, it seems that the individual variations of the

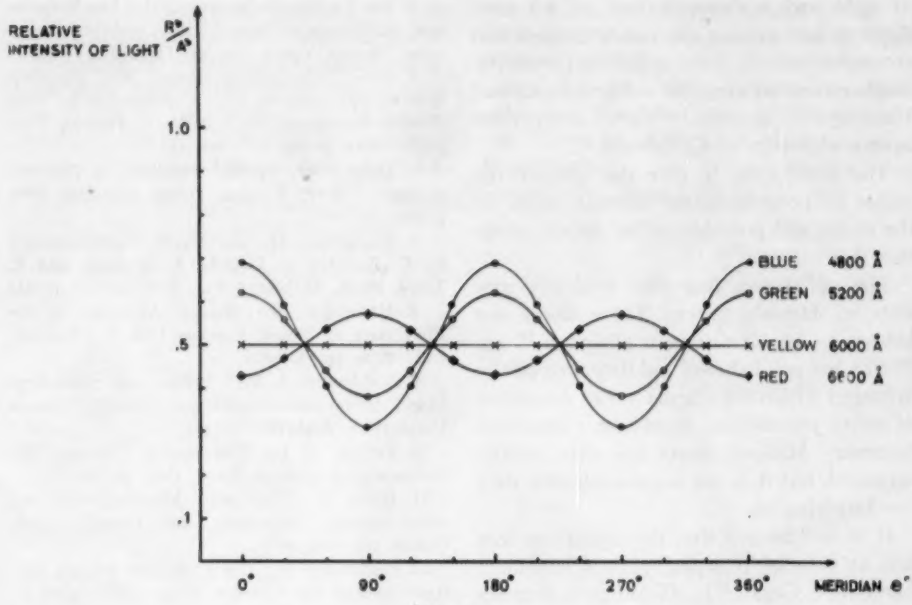

Figure 2

thickness of the retarding plate are not very great.

If the interference theory is correct, it must be possible to change the colors of Haidinger's brushes by a retarding plate inserted between the polarizer and the eye. This experiment is rather difficult to perform because a retarding plate behind the polarizer makes the brushes indistinct and it is thus not easy to discern the colors.

The best results are achieved with the clouded sky as the source of light. It is not practical to rotate the polarizer. Instead of this, the observer looks alternately through two polarizers with their optic axes at right angles. Treble layers of cellophane are used as the retarding plate. The angles between the optic axes of the polarizers and that of the cellophane are 45 and 135 degrees, respectively. With these arrangements I saw Haidinger's brushes in purple and yellowish green. I repeated the experiment on a small number of trained observers. Of three subjects with normal trichromatic vision who did not know the expected result, two saw the brushes in purple and green; the third was not able to discern the colors. A fourth subject, who is deuteranomalous, was able to see the purple sectors but not the green ones.

The combination of a radial analyzer with a radial retarding plate explains Haidinger's brushes satisfactorily. There remains the question of the anatomical basis of the phenomenon.

No explanation of Haidinger's brushes is feasible without the supposition of an analyzer in the eye. All the current hypotheses, with the possible exception of that of Cogan, hold that this analyzer is radial.

The parallax experiment of Gullstrand had previously been performed by Dimmer [28] with a quite different result. According to Dimmer, Haidinger's brushes move with the vascular shadows. I have repeated the experiment according to both the methods used by Dimmer and Gullstrand, which differ slightly, but did not achieve any conclusive result. Haidinger's brushes, the entoptic fovea, the entoptic macula, and the vascular shadows are not very easily seen, and it is difficult to observe their parallactic displacements. Using the sky as the source

of light and a stenopeic hole of 1.5 mm. diameter and looking alternately through two crossed polarizers, I saw a distinct parallactic displacement between the entoptic fovea and Haidinger's brushes. This observation agrees with that of Gullstrand.

The conclusion is that the site of the radial analyzer is in the deepest layers of the retina and probably in the retinal receptors themselves.

The radial retarding plate probably consists of Henle's fibers. These fibers are known to be birefringent (Dimmer,[23] pp. 95-97) but not dichroic, and they are radially arranged within the macula lutea. A number of other possibilities should be considered, however. Müller's fibers are also radially arranged, but it is not known whether they are birefringent.

It is well known that the crystalline lens acts as a radial retarding plate (Schmidt,[24] Lenhard,[25] Cogan [20]). Haidinger's brushes are, however, clearly visible to an aphacic eye (Boehm,[26] Forster [27]).

The cornea also acts as a radial retarding plate (Schiötz,[28] Nordenson [29]), but the birefringence is very small.

Summary

After a discussion of several previous explanations, a model of Haidinger's brushes based upon the interference theory is described. The interference theory is discussed, and certain differences between the model and Haidinger's brushes are explained. The paper is concluded by a brief discussion of the anatomical basis of the phenomenon.

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Uveitis in Association with Rheumatism

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This paper is concerned with the general manifestations of rheumatic diseases and their relationship to inflammations of the uveal tract. Its purpose is to present information on these diseases and to describe their association with the ocular disease as simply and briefly as is consistent with adequate coverage. It is our belief that inadequate attention has been paid to uveitis-arthritis syndromes in the American literature and that new attention should be focused on this aspect of uveitis in order to enable the ophthalmologist to systematize his thinking with regard to evaluation of the various uveitis cases he encounters in order to work with the general physician in their management. In spite of the lack of complete knowledge of the etiology of a number of forms of arthritis which are to be discussed, it is important to recognize their relationship to uveitis for the following reasons:

1. If one can recognize the characteristic ocular clinical manifestations in a patient who has arthritic symptoms he may save the patient considerable time and expense.

2. If the disease is recognized early proper therapy may be instituted and serious complications prevented.

The term "rheumatism" refers to a group of diseases which exhibit pain and stiffness of joints, muscles, ligaments, and related structures. These disorders may be localized to the joints and associated structures or be combined with widespread disease of various organs. Some of the rheumatic group of diseases, such as rheumatoid arthritis and Reiter's syndrome, frequently exhibit ocular disease, while others, such as gout, osteoarthritis, and specific infectious arthritis, rarely exhibit associated eye lesions.

Of the chronic diseases, rheumatism ranks first in incidence and is second only to nervous and mental disorders as a cause of disability.[1] Mettier[2] estimated that these diseases cause more than 300,000 persons to become unemployable in the United States annually. It must be pointed out that these figures refer to the more serious forms of the disease and that the ocular manifestations may occur with milder or even unrecognized joint disease.

Classification of Rheumatic Diseases

For the purposes of this presentation the classification of the American Rheumatism Foundation may be abbreviated as follows:

1. Infectious arthritis (tuberculosis, brucellosis, syphilis, pneumonia)
2. Arthritis in rheumatic fever
3. Rheumatoid arthritis
   (*a*) multiple } adult;
   (*b*) vertebral } childhood (Still's disease)
4. Gouty arthritis
5. Symptomatic
   (*a*) Reiter's syndrome
   (*b*) Behcet's syndrome
   (*c*) Psoriasis

Many other diseases and conditions are associated with arthralgia or frank arthritis, but the association is of rare occurrence, and it is not the purpose of this presentation to list or discuss all causes. In following the above classification, certain forms of the disease will be mentioned briefly while the more important ones will be discussed in more detail. A summary of our experiences with a group of these syndromes will supplement the discussion. The following groups will be discussed in the order of their importance.

Rheumatoid Arthritis and Iritis.—Rheumatoid arthritis is a disease of unknown cause. It occurs principally in temperate climates, has a familial tendency, and develops in persons between the ages of 25 and 50 in about 80% of cases. The peak occurrence is between the ages of 35 and 40 years. It affects females in a ratio of 3:1

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(except in rheumatoid spondylitis, where males outnumber females 10:1). A clear-cut explanation of these ratios is not available, and recent speculations have linked this disease with the so-called collagen diseases, postulating that some agent is capable of causing changes in the ground substances of tissues.

In the majority of the patients the disease begins insidiously, with peripheral involvement, often in one or more joints, and with swelling and pain. Other joints may subsequently become involved. There may be comparatively little systemic involvement at this time. Other cases commence with slightly more violence, and the attacks of joint disease are accompanied with constitutional disturbances such as fever, tachycardia, leukocytosis, elevated sedimentation rate, lymphadenopathy, and splenomegaly. Rarely the disease begins with an acute polyarthritis and severe systemic manifestations.

In the average case the joint involvement is symmetrical, with involvement of the hands and extremities, but in severe cases all joints may become involved. Thickening of the periarticular tissues and atrophy of the proximal and distal muscles leads to a fusiform or spindle-shaped appearance of the joints. The joint disease may become arrested or quiescent at any stage, but at times it proceeds to a chronic stage which leads to persistent contraction and deformity. In the advanced stages fibrous and bony ankylosis occur.

Pathologically the inflammatory changes in the joints result in hypertrophy of the synovial membrane, with formation of villi and increased production of fluid. The adjacent ligaments may be affected. After repeated attacks adhesions form in the joint cavity and the cartilage is destroyed. In the spine the discs show early atrophy and there is narrowing of the intervertebral spaces. Bone gradually replaces the disc, and the ligaments may become calcified.

Subcutaneous nodules occur in 15% to 20% of cases, especially at the sites of pressure over bones; they may be present for a short period or persist permanently. They are often found over the ulna distal to the olecranon process, and they vary in size from tiny seed-like masses to areas measuring 2 to 3 cm. The nodules are composed of foci containing central necrotic zones (which may become caseous or liquified) surrounded by a zone of cells with the axis arranged at right angles to the central necrotic area and composed of fibroblasts and an outer enveloping zone of granulation tissue containing a variable amount of fibrous tissue. These nodules are often seen in skeletal and cardiac muscle tissue, and at times they occur in the anterior sclera, giving rise to the condition known as sclero-malacia perforans.

The diagnosis may be difficult in acute febrile polyarticular or monarticular arthritides, but the criteria have now been well established, and it is possible to distinguish this disease in most instances from other forms of arthritis. Degenerative joint disease is the most important rheumatic affection which must be differentiated from rheumatoid arthritis. In the latter the patient is ill and exhibits systemic manifestations, whereas in degenerative disease the patient is completely well except for the joint manifestations.

Still's disease, Felty's syndrome, psoriatic arthritis, and rheumatoid spondylitis are variants of this disease, and they cannot be clearly separated from rheumatoid arthritis. Most observers accept Still's disease in children (juvenile rheumatoid arthritis) as being identical with rheumatoid arthritis of the chronic progressive type in adults. Patients with Felty's syndrome usually have a severe form of rheumatoid arthritis with marked systemic manifestations, including hepatomegaly, splenomegaly, and leukopenia. Psoriasis occurs in about 3% of cases of rheumatoid arthritis; however, the joint changes are characteristic of rheumatoid disease. Ankylosing spondylitis, Marie-Strumpell arthritis, and rheumatoid spondylitis are synonymous terms, regarded by many as typical rheumatoid arthritis of the spine. About 20% of these patients have peripheral joint involvement characteristic of rheumatoid arthritis. The association has suggested that the vertebral involvement may be a special form of the disease. There are, however, some differences, primarily that males are affected in a ratio of 10:1 over females, in contrast to the situation in rheumatoid arthritis. The response to therapy also differs in that the vertebral disease responds to radiation therapy but fails to respond to gold therapy.

The prognosis in joint cases has not been accurately assessed. Approximately one-third of the cases seem to progress and develop more or less severe crippling deformities. The remainder of cases undergo prolonged remissions or improvement or remain unchanged.

The general treatment is directed towards improvement of the well-being of the patient by the institution of rest, watching the general nutrition, physical therapy, and drug therapy. Salicylates are invaluable for relief of pain, and recent therapeutic studies have been directed toward evaluation of steroid therapy alone and in combination with salicylates. The general concensus is that steroid therapy should be reserved for progressive and severely crippling forms of the disease and for the chronic progressive forms of iritis.

Rheumatoid Iritis.—It seems to be well established in the minds of ophthalmologists and rheumatologists that the coincidence of iritis and iridocyclitis in patients with rheumatoid arthritis is of such frequency that both must be considered as secondary to the same agent. Up to 1946 remarkably little information was available as to the incidence of iridocyclitis in the various forms of rheumatoid arthritis. During this year two reports, by Franceschetti [3] and by Sorsby and Gormaz,[4] indicated the general incidence of iritis in various rheumatic infections. The latter authors found 15 cases showing iritis out of 332 cases of peripheral joint rheumatoid arthritis, an incidence of approximately 5%. Because of the much higher incidence of the disease in females many more cases of iritis were observed in this sex. In the same series of cases 3 out of 53 cases of rheumatoid spondylitis (spondylitis ankylopoietica), approximately 6%, showed iritis, and out of 7 cases of Still's disease there were no cases of iritis. A significantly higher incidence of iritis was noted in the rheumatoid group of cases than in a large control group of females. Mills [5] published a review of the findings in 42 patients with iritis which were found among 600 cases of rheumatoid arthritis at the Massachusetts General Hospital. In 29 (5%) of these cases no other possible alternative etiology could be found for the disease; therefore, a direct association between the iritis and arthritis was assumed. Godtfredsen [6] gives figures, presumably from the literature, as to the incidence of iritis in various types of rheumatic diseases, and of the forms of rheumatoid arthritis he states that 2% to 5% of patients with peripheral joint disease, 20% of those with Still's disease, and 15% to 50% of those with ankylosing spondylitis develop iritis.

Clinical Manifestations: The iritis which accompanies rheumatoid involvement of the peripheral joints and spine has been observed by us and others to pursue several courses.

1. Acute rheumatoid iritis. This form may precede the onset of joint involvement by as much as two to four years, but it most commonly is associated with or follows it. Birkbeck et al.[7] emphasized that young males may complain of mild backache and stiffness but not regard it seriously enough to seek assistance. This group may develop iritis, and it is only by questioning or by x-ray examination that the presence of joint disease is revealed. These authors found that 13 out of 148 (8.5%) sufferers from ankylosing spondylitis had iritis. We have had a similar experience in a number of cases, and, while the exact correlation between the two is not established, the incidence is such that, in the absence of other specific diagnosis, one should consider rheumatoid disease as the cause. Most attacks are unilateral, and affect either eye; commonly one eye may be affected by recurrent attacks at irregular intervals. The intensity of the attacks varies considerably, some patients consistently having mild ones and others having severe fulminating ones (Fig. 1). The average attack lasts two to four weeks, unless treated with oral or topical corticosteroids, to which the attacks respond readily. Great variation is noted in the sequellae of the attacks. Some eyes with severe inflammation, coagulated exudate in the anterior chamber (Fig. 2), and a fixed pupil clear completely, while in others with a less intense inflammation posterior synechias tend to form (Fig. 3). The intensity of the inflammation, or exacerbations, seems to have little relation to the severity of the joint disease, or relapses of joint disease. Many cases develop large numbers of fine anterior vitreous opacities, indicating the presence of cyclitis. Keratic precipitates may or may not be present; if so, they are usually round, white, and located in the usual pattern on the lower cornea. Elevation of the intraocular pressure is rare in such cases. An occasional development is the occurrence of papillitis, secondary to the acute anterior inflammation. In association with this edema may occur in the macula and result in cystic degeneration and reduced vision. It is interesting that choroiditis practically never occurs in rheumatoid disease, the selective involvement of the iris or iris and ciliary body being remarkable.

These attacks of acute or subacute iridocyclitis may occur in one or the other eye at intervals of 3 to 12 months for years.

Fig. 1.—Acute rheumatoid iritis, bilateral.

Fig. 2.—Plastic iritis, rheumatoid.

Fig. 3.—Acute rheumatoid iritis.

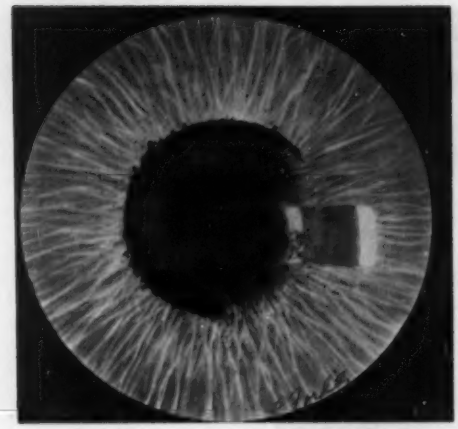


Fig. 4.—Chronic rheumatoid iritis.

In general, those patients with relapsing or progressive rheumatoid disease tend to have continuing attacks and those with inactive disease remain well. Some patients with chronic progressive ankylosing arthritis and recurrent iritis develop the following form of ocular disease.

2. Chronic rheumatoid iritis. This type seems to be associated with the severer forms of arthritis of the peripheral and vertebral joints which exhibit ankylosis and deformities. An occasional case, however, occurs in patients with disease limited to the spine. The ocular disease is bilateral, of low-grade intensity, relentless in its activity, and unaccompanied by congestion or inflammation (Fig. 4). It is unaffected, or modified very slightly, by any form of therapy, including corticotropin (ACTH) and the corticosteroids. Synechias and a pupillary membrane almost always develop, and the trabeculae gradually become blocked. Glaucoma and cataract are frequent, and the prognosis for ultimate vision is extremely poor. In those cases where the condition is recognized early, prolonged oral and topical therapy with corticosteroids may result in sufficient subsidence to delay or prevent severe complications. The uveitis may persist for years before burning itself out.

If glaucoma develops in such cases it may be controlled with the usual antiglaucoma drugs in the early stages, but surgery in the form of an iridectomy, filtering procedure, or cyclodiathermy may become necessary (Fig. 5). If the disease has existed for some time, and cataract extraction becomes necessary (Fig. 6), the prognosis is extremely poor, because the eye seems to wilt after even the most successful extraction.

Pathology: In the acute stages there is an intense iritis or iridocyclitis, with round-cell infiltration (Figs. 7, 8). The disease may subside without damage or lead to marked atrophy with posterior and anterior synechias.

Rheumatoid scleritis is characterized by intense inflammation of the sclera and adjacent uvea, with nodule formation (Figs. 9, 10, 11).

Still's Disease.—In 1897 Still [8] demonstrated that rheumatoid arthritis does occur in children but that the disease seems to differ in both its clinical aspects and its anatomy from adult rheumatoid arthritis. Present-day observers regard it as identical with the adult form. This disease is not common, and it occurs somewhat more com-

Fig. 5.—Chronic rheumatoid iritis, iridectomy.

Fig. 6.—Chronic rheumatoid iritis.

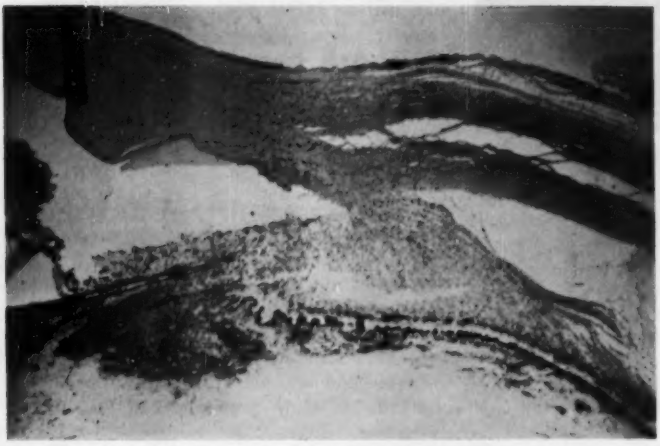


Fig. 7.—Rheumatoid iridocyclitis.

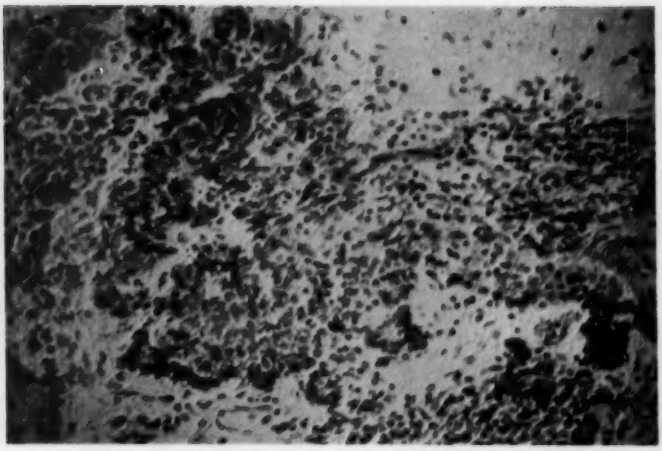


Fig. 8.—Rheumatoid iritis.

Fig. 9.—Rheumatoid scleritis.

monly in females. The onset usually is insidious, usually before the second dentition. Occasional cases, however, have an acute febrile onset. Among the distinguishing clinical features of juvenile rheumatoid arthritis include a tendency for the children to show severer systemic signs, with spiking temperature and leukocytosis. Coss and Boots [9] found splenomegaly in 30%, hepatomegaly in 23%, and lymphadenopathy in 60% of 56 cases. The knees, wrists, and cervical spine are particularly affected, and epiphyseal damage frequently leads to dwarfism and deformity.

Sury [8] studied 151 cases of juvenile rheumatoid arthritis in Copenhagen. Chronic iridocyclitis was found in 21 patients (15%). In 14 cases (9%) a band-shaped keratitis was present (Figs. 12, 13). In most instances the ocular disease follows the onset of the joint disease, but in two of Sury's cases it preceded the onset by about a year.

In most cases the disease has an insidious onset in the eyes, with or without congestion, marked blurring, and photophobia. In some cases the disease is only diagnosed in the eye by careful examination and slit lamp microscope study. Once established, it tends to persist as a low-grade plastic iritis. It is most often bilateral, being so in 9 of 14 cases reported by Franceschetti [10] and 28 of 34 cases reported by Vesterdahl and Sury.[11] It persists in a chronic form for months or even years, usually leading to cataract formation. About 50% of the cases eventually develop moderate to severe reduction in vision.

The statement has been made that the eye lesions may precede onset of the joint manifestations. François and Haustrate [12] state that any child with the characteristic ocular changes and without arthritis should be examined carefully for any sign of arthritis and extra-articular lesions. The sedimentation rate and antistreptolysin titer should be checked. If they are accelerated or high,

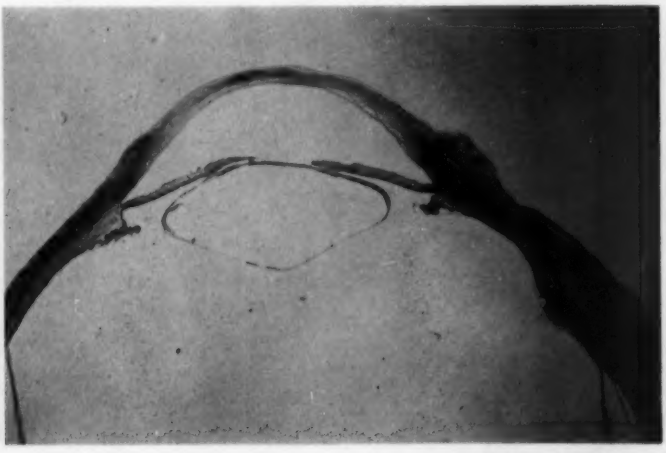


Fig. 10.—Rheumatoid scleritis.

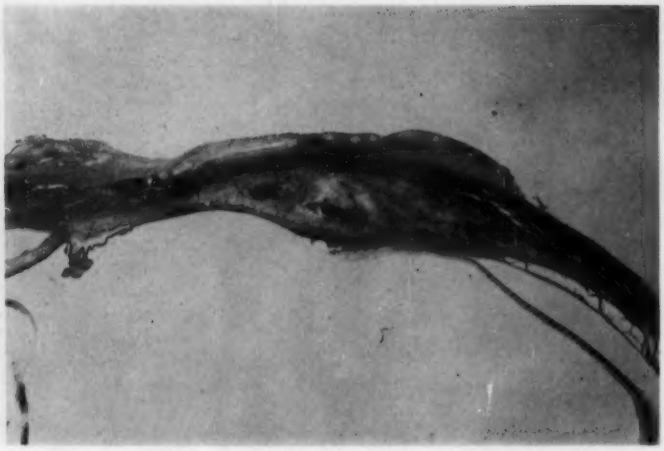


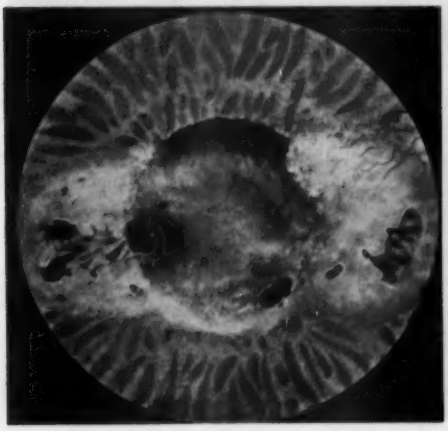
Fig. 11.—Rheumatoid scleritis.

one should be suspicious of juvenile rheumatoid arthritis.

The general management of these cases is the same as for the adult form of the disease. This chronic form of the disease responds only moderately to corticotropin and corticosteroids, but such therapy should be instituted in an attempt to prevent complications.

Gout.—According to the Primer on the Rheumatic Diseases,[13] gout is a metabolic disease of unknown causation characterized by (1) acute attacks of arthritis with complete remission between attacks; (2) increased concentration of uric acid in the serum and body fluids; (3) eventual deposition of sodium urate crystals in articular, periarticular, and subcutaneous tissues, bone, and sometimes also in the urinary tract, and (4) degenerative changes, particularly in the vessels of the kidneys in many patients who have had the disease for years. The disease may limit itself to acute attacks of arthritis which resolve completely (acute gouty arthritis) or progress over the years to a stage in which numerous deposits of sodium urate crystals (tophi) are present (chronic tophaceous gout). In gout there seems to be a hereditary disturbance of uric acid metabolism, and hyperuricemia is commonly found in the asymptomatic kin of gouty patients; in males it is commonly detected at some time after puberty, and in females, at or after menopause. Ninety-five per cent of the clinical cases occur in males, possibly because of the longer duration of the hyperuricemia in this sex. The first symptoms usually appear between the second and seventh decades. Uric acid is an end-product of purine metabolism and is a threshold substance, excretion depending on the blood level, although the clearance in persons with gout is reduced. The helix, antihelix, tendons, tarsal plates, olecranon, and patellar bursae may be involved by tophi.

Fig. 12.—Band keratopathy, Still's disease.



The diagnosis is usually simple in acute attacks but difficult in the chronic stage. A family history of gout, calculi in the urine, a history of acute gout, an elevated serum uric acid level in the absence of renal impairment, a response to colchicine, and the presence of tophi suggest the diagnosis. The blood urea N or N. P. N. should be determined to differentiate hyperuricemia due to gout from that due to renal disease. Bone x-rays are not typical.

The usual treatment consists in the use of colchicine, salicylates, a low-purine diet with

Fig. 13.—Band keratopathy, Still's disease.

high carbohydrate and low fat intake, and a large fluid intake. Corticotropin and corticosteroids are also effective in the control of the acute manifestations of the disease. Male children of gouty patients should be checked for hyperuricemia.

Gouty Iritis.—The exact frequency of iritis in gout has never been determined; in fact, some observers favor the opinion that the occasional case of iritis in a gouty patient is probably of other origin. The large series of gouty patients which have been reported in recent years fail to mention iritis as a complication. However, recurrent attacks in gouty patients, especially when associated with renewed activity in the joints, suggest the possibility of an association. The response to colchicine and salicylates also suggests that the two are related. Hughes [14] states that in persons predisposed to attacks of gout a dietary indiscretion such as a large intake of purines, fat, or alcohol may precipitate an attack, with an associated episcleritis or iritis. The ocular symptoms begin suddenly in one eye with a subacute or acute inflammatory reaction, with a heavy exudate into the anterior chamber (plastic iris and pupil (Fig. 14)). The acute iris and pupil (Figs. 14, 15). The acute phase of the disease lasts two to three weeks in the average case, but with active treatment it can usually be brought under rapid control in three to four days. Colchicine, 0.5 mg., can be given in a dose of 2 tablets every two hours until the joint and eye symptoms are relieved or gastrointestinal symptoms appear (nausea, vomiting, or diarrhea). A

Fig. 14.—Gouty iritis.

second course may be necessary. Cortisone or hydrocortisone in the usual doses will also produce a rapid subsidence of the symptoms. If a positive diagnosis of gout cannot be made, and if one suspects gout, a therapeutic trial with colchicine is indicated. A prompt response is suggestive that the iritis is due to gout.

Acute Rheumatic Fever.—Ocular symptoms are rarely encountered in this disease, which is unusual considering its probable infectious origin. Examinations of series of patients with acute rheumatic fever have failed to reveal either anterior or posterior ocular lesions. One of us (M. J. H.), however, has seen a series of cases of acute rheumatic fever in older children and teenagers and had the opportunity to examine the fundi carefully. At least five of these cases (without bacteremia or detectable valvulitis) showed foci of acute choroiditis which were localized, yellowish, and deep in position. They did not affect the retina or its epithelium. They greatly resembled miliary tubercles. Resolution occurred without scar formation, conjointly with subsidence of the acute phase of the arthritis. Coburn [15] reports iritis as occurring once in a series of 162 cases of rheumatic fever, and the iritis recurred, with relapse of the joint disease. Pillat [16] found small fresh or old choroidal lesions in 17 of 28 cases of rheumatic fever; most of these were in the peripheral choroid, but in two instances the lesions looked like miliary tubercles. It is difficult to explain the absence of eye lesions in some series of cases and their presence in others. It is possible that the more violent cases of rheumatic fever do show choroidal foci; certainly the patients seen by one of us were desperately ill.

A prompt response of the eye and systemic manifestations to salicylates would tend to confirm the diagnosis of rheumatic fever as compared with rheumatoid arthritis and other syndromes.

Reiter's Syndrome. — Numerous reports on this syndrome have appeared in the literature from the entire world. The majority of reports present the usual group of symptoms which characterize this disease, namely: conjunctivitis, urethritis, and arthritis. There is, however, no accurate agreement on the limits of the group of symptoms which should be encompassed within this syndrome.

The disease is usually found in young men, and urethritis is the commonest presenting symptom. Many cases first develop arthritis as the most common initial symptom, and others first exhibit conjunctivitis. Less common symptoms include stomatitis, transient diarrhea, cutaneous lesions, and iridocyclitis. In the majority of cases the patients recovered within two to six months. The joint manifestations may resemble those seen in rheumatoid arthritis, with a sudden onset in symmetrical joints. Those of the lower extremities are more frequently involved, and large ones rather than small. Most cases have polyarticular involvement with pain, swelling, increased temperature, and effusion. Permanent restriction of movement, deformity, and ankylosis may occur. The urethritis is characterized by a mucopurulent discharge, and routine cultures of the exudate show no specific organisms. Conjunctivitis is the commonest ocular manifestation and is of a purulent type, with negative cultures.

The etiology of this syndrome is in doubt, and numerous investigations have failed to demonstrate conclusively a definite agent.

Ocular Involvement: The conjunctivitis has been investigated adequately by a number of authors. Most examinations of smears and cultures have been negative for a bacteriologic agent or a virus. Thygeson [17] was not able to demonstrate a viral agent after a complete study of two cases.

Iridocyclitis has been observed by us in three cases of this syndrome. One of the cases commenced with the typical manifestations and later developed joint inflammation more characteristic of rheumatoid disease, associated with iridocyclitis. He has been followed for five years and has had recurrent attacks of iridocyclitis and moderate exacerbations of the joint disease, without urethritis. The two other cases of this syndrome have had recurrences of the urethritis, arthritis or arthralgia, and acute biliteral iridocyclitis almost every year for three years. Repeated studies of material from these cases have failed to reveal an etiologic agent.

Specific treatment for this type of disease has not been developed. The ocular lesions last two to four weeks, then subside spontaneously. The usual treatment for iridocyclitis is recommended. Our cases have not responded particularly well to local corticosteroid therapy.

Behcet's Syndrome (Recurrent Uveitis with Mucocutaneous lesions; Aphthous Uveitis).—This condition was first described in the Mediterranean area by Adamantiades [18] and first recognized as a syndrome

by Behcet, a Turkish dermatologist. It affects young persons between the ages of 20 and 30 in most instances, and evolves slowly over a period of years. The sexes seem to be affected equally.

The uveitis is recurrent and bilateral, usually affecting one eye at a time. In the early stages the inflammation is mild and transient, but as the condition develops the attacks become more violent and lead to progressive visual deterioration. A diffuse uveitis occurs, but the anterior segment seems to be principally affected. Vitreous opacities may be extensive. The attacks last two to three weeks, and recurrences often take place at fairly fixed intervals. Hypopyon is not evident in the early stages, but after several years it may appear. Sooner or later visual damage becomes permanent because of vitreous opacities, cataract, glaucoma, and atrophy of the eye.

The disease is usually associated at its onset with a number of systemic manifestations, which include aphthous stomatitis, male and female genital herpes, a number of skin conditions (dermatitis herpetiformis, erythema nodosum, papulopustular erythema), and at times migrating thrombophlebitis.

Rheumatoid pains, true arthritis, or intermittent hydrarthroses may occur, but these are of minor importance in this disease.

Sezer has recently published a report which includes case reports and the results of attempts to isolate a microbiologic agent. He reported isolation of a virus from the vitreous in a typical case.[19]

Uveitis Due to Microbial Agents.—A detailed discussion of infectious uveitis is beyond the scope of this paper, and the important aspects of many of the forms have been admirably presented by Woods. It is our intent only to stress the joint-eye manifestations; therefore the discussion will be limited to a brief presentation of those diseases having joint lesions and in which uveitis also is encountered with modest frequency.

A. Gonococcic Arthritis: The incidence of this disease and its complications has decreased enormously since the advent of antibiotics, particularly penicillin. Most cases of gonorrhea are cured by the patient or the general physician prior to invasion of synovial or uveal tissues. Unless some unexpected change should occur in the gonococcus, or in human resistance, the incidence of ocular complications should drop to insignificant levels.

B. Brucellosis: In countries and states where brucellosis is incompletely controlled or where accidental outbreaks occur, an occasional case of brucellar arthritis and uveitis is to be expected. In Mexico, where Brucella melitensis infections are commoner, Puig Solanes et al.[20] found uveitis to occur in only 6 cases of 413 cases of active brucellosis. Only a modest number of cases with joint disease ever develop uveitis. Therefore the relationship of these two complications is uncommon, and in most patients with joint and uveal disease the possibility of concomitant brucellosis is remote indeed. In a survey of more than 1400 patients with various types of uveitis we have encountered but one case of brucellosis. It might be added that the laboratory investigations on our cases have been done by Dr. Karl Meyer, Hooper Foundation, University of California School of Medicine. He has been active in investigations on brucellosis in animals and humans for many years, and we have been fortunate to have his advice in our uveitis survey.

C. Tuberculosis: The incidence of tuberculosis of the bones and joints has declined markedly in this country during the past 15 years. Nevertheless, about 4% of patients with tuberculosis develop such complications. It is uncommon, however, for those patients with pulmonary tuberculosis and joint disease to exhibit uveitis. Those with tuberculosis of the bones and genitourinary tract in the absence of pulmonary lesions seem to have a higher incidence of uveitis. In our fairly large series of cases, however, there is not an instance of active tuberculous arthritis or spondylitis which could be related to disease of the uveal tract. Several cases of uveitis have been seen in persons with remote tuberculous joint infections, but no relationship could be established. The infrequency of associated tuberculous bone and joint disease and uveal tract infections in areas where the former is common (Alaska) suggests, at the present time, that a relationship between the two is unlikely.

D. Syphilis: In more than 1400 cases of uveitis surveyed since 1947, we have encountered but 1 positive Wasserman test. Therefore the relationship and incidence of syphilitic uveitis and joint disease are not of particular consideration in this discussion. It might be assumed that occasional cases of syphilis have been seen which were seronegative and that therapy might have estab-

lished the diagnosis. It is, however, difficult to believe that many cases could have been missed. Also, the infrequency of undiagnosed joint manifestations in our series of cases is such that syphilis probably could be excluded.

E. Toxic, and Infectious, Uveitis: A number of other conditions, such as Stevens-Johnson syndrome, lupus erythematosus, viral diseases (measles, chickenpox), influenza, and streptococcic infections, may have associated joint-uveal tract inflammations. The systemic disease is usually evident in such cases, however, and the uveal inflammation is shortlived, nonrecurrent, and not a particularly important diagnostic problem.

Psoriatic Arthritis.—The association between psoriasis and arthritis of the rheumatoid type has been discussed by many investigators. It must be concluded, after review of many articles and evaluation of criteria set forth for diagnosis of the arthritis in this group of cases, that proof is lacking that psoriatic arthritis is a specific entity. Iritis might be expected to occur in an occasional patient with such skin and joint manifestations.

Comment

The following Tables 1 and 2 present in brief the observations made on 43 patients with joint disease and associated uveal inflammation.

It can be seen from Table 1 that, of the two general types of rheumatoid iritis, there were 3 patients with chronic bilateral iritis and 35 patients with acute recurrent iritis. Some of these patients had negative x-rays, but in most instances their disease was of short duration and x-ray evidence was not present. In such cases the association of a general illness with malaise, fever, leukocytosis, and elevated sedimentation rate, hepatomegaly, and splenomegaly served to convince us of the nature of the illness. In

TABLE 1.—*Cases of Rheumatoid Arthritis with Iritis*

Case	Age	Sex	Eye	Attacks, No.	Joint Disease	X-Ray	Comment
1	35	M	R	1	Peripheral	0	Recurrent arthritis & myositis
2	38	M	R&L	7	Vertebral	+	Ankylosis, spine & sacroiliac
3	22	M	R&L	R 5 L 1	Vertebral & peripheral	+	Typical rheumatoid
4	28	M	R	1	Peripheral	0	Recurrent arthritis, hands & lower extremities
5	28	F	R	2	Vertebral & peripheral	+	Acute eye disease
6	29	M	R&L	Many, 10 yr.	Vertebral & peripheral	+	Acute eye disease
7	29	M	R&L	5	Back and hips	+	Acute eye disease
8	30	M	R&L	7	Vertebral & sacroiliac	+	Acute eye disease
9	30	M	L	1	Vertebral & knees	0	
10	32	M	R&L	Chronic, 2 yr.	Vertebral & peripheral	+	Severe crippling
11	32	M	R&L	Chronic, 6 yr.	Vertebral & peripheral	+	Severe crippling
12	32	M	L	2	Vertebral	0	Probable rheumatoid
13	33	M	R&L	2	Vertebral	0	Probable rheumatoid
14	34	M	R&L	1	Fingers, hands, & sacroiliac	0	Probable rheumatoid
15	37	M	R&L	6	Vertebral	Not done	Stiff lower spine
16	39	M	R	1	Peripheral	0	Psoriasis, elevated sedementation rate
17	39	F	R&L	30	Vertebral	+	Spinal ankylosis
18	40	M	R&L	3	Peripheral & vertebral	+	
19	41	F	R&L	3	Peripheral	0	
20	41	F	R&L	50	Peripheral & vertebral	+	
21	43	M	L	1	Vertebral	+	
22	43	F	R&L	30	Peripheral	+	Typical rheumatoid
23	45	M	R&L	20	Vertebral & peripheral	+	Typical rheumatoid
24	46	M	R	2	Vertebral	+	Ankylosis
25	48	M	R&L	3	Peripheral	0	Probable rheumatoid
26	49	M	R&L	5	Vertebral	+	Typical rheumatoid
27	50	M	R&L	3	Vertebral	+	Typical rheumatoid
28	50	M	R&L	7	Vertebral	+	Typical rheumatoid ankylosis
29	50	F	R&L	3	Vertebral	+	Typical rheumatoid
30	51	F	R&L	30+	Vertebral	+	Typical rheumatoid ankylosis
31	52	M	R&L	5	Vertebral	+	Typical rheumatoid
32	40	F	R&L	6	Vertebral	Not done	Probable ankylosis
33	54	M	R&L	Chronic, 20 yr.	Peripheral & vertebral	+	Typical ankylosis
34	54	M	L	4	Vertebral	0	Probable ankylosis
35	58	M	R&L	31+	Peripheral	+	Typical ankylosis
36	60	M	R&L	9	Vertebral	Not done	Typical ankylosis
37	62	M	R&L	14	Vertebral	0	
38	61	M	R&L	27	Vertebral	+	Typical ankylosis

TABLE 2.—*Other Forms of Arthritis with Iritis*

Type	Age	Sex	Eye	Attacks	Joint Disease	X-Ray	Comment
Still's	8	F	R&L	Chronic	Vertebral & peripheral	+	Severe crippling arthritis, cataract O.D.
Reiter's	24	M	R	2	Vertebral	0	Recurrent urethritis, arthritis, iritis
Reiter's	27	M	L	4	Vertebral	+	Recurrent urethritis, arthritis, iritis
Rheumatic fever	39	F	R	2	Peripheral	0	Recurrent rheumatic fever (probable)
Gout	60	M	L	Many, 12 yr.	Peripheral	+	Proved gout, eyes active with relapse in joints

a number the disease involved only the lower spine and was not evident to the patient. We believe that x-rays of the sacroiliac joints are important for revealing the presence of unrecognized rheumatoid disease.

One should also always consider the possibility of rheumatoid disease in a patient who has the typical iritis and some systemic manifestations, even though joint disease cannot be detected. In our experience and that of others the uveal inflammation may precede development of joint disease by as long as one to four years. The same may be stated for children with Still's disease, and we have seen a number of cases with the typical ocular manifestations but which have not as yet shown any sign of inflammation of the joints.

One of the patients with Reiter's syndrome had typical manifestations at the onset but later developed all the manifestations of rheumatoid disease of vertebral and peripheral joints in association with recurrent attacks of iritis. The second patient with Reiter's syndrome developed recurrent attacks of urethritis, arthritis and iritis.

Table 3 summarizes the findings in the total series of cases.

Summary and Conclusions

The occurrence of acute iritis of a recurring type should always lead to investigations for evidence of associated joint disease. The frequent association of the two conditions is more than a chance occurrence. Patients may have unrecognized chronic arthritis of the spine which can only be detected by careful examination and x-rays. Fever, elevation of the sedimentation rate, hepatomegaly, splenomegaly, and leukocytosis may help in establishing the final diagnosis.

Rheumatoid iritis occurs in two forms: an acute recurrent one, often affecting one or both eyes, and a chronic one affecting both eyes. The acute variety responds rapidly to topical corticosteroid therapy, whereas the chronic one does not respond to any type of treatment. The chronic form occurs most often in the severer type of joint disease. Ocular involvement may precede onset of joint disease by as much as one to four years.

Juvenile rheumatoid arthritis (Still's disease) frequently has an associated chronic bilateral iritis which persists in spite of treatment and leads to band keratopathy and cataract.

Reiter's syndrome may have an associated iritis of recurrent type. The joint and eye disease may assume the characteristics of rheumatoid disease with time.

Thirty-eight cases of rheumatoid iritis are described. Thirty-five were of the acute and three were of the chronic type. One case of juvenile rheumatoid iritis (Still's disease) is presented. Two cases of Reiter's syndrome and one case of gouty iritis are also presented. The patient with gouty iritis had relapses of iritis in association with exacerbation of joint disease.

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TABLE 3.—*Cases of Joint Diseases with Iritis*

		Joint Involvement			Sex		Eye Involvement				
	Cases	Vertebral	Peripheral	Both	M	F	R	L	Bilat.	Acute	Chronic
Rheumatoid arthritis & iritis	38	18	7	13	30	8	3	4	29	35	3
Still's disease	1	--	--	1	--	1	--	--	1	--	1
Reiter's disease	2	2	--	--	2	--	1	1	--	2	--
Gout	1	--	1	--	1	--	--	1	--	1	--

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Effect of Certain Drugs on the Iris Vessels

The Action of Isoflurophate and Homatropine on the Rat's Eye

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The intravenous injection of drugs or their topical application on the eye may produce changes in the ocular blood vessels. However, it has been very difficult to evaluate the action of a particular drug on the vessels, even with the most acute ophthalmoscopic and slit-lamp observations or photographs of the vessels.

Zeller[1] believed that physostigmine might cause either a hyperemia or a constriction of conjunctival vessels. Colle, Duke-Elder, and Duke-Elder[2] studied the iris vessels with a slit-lamp in animals given intravenous injections of a variety of materials. These investigators used albino rabbits because eye pigment in animals other than albinos obscured the vessels. In general, they could estimate whether a vessel underwent constriction or dilatation. More recently, Leopold and Comroe[3,4] and Von Sallman and Dillon,[5] studying the effect of topically applied isoflurophate (DFP), suggested that this material caused a dilatation of capillaries as well as arterioles.

The present study arose from a desire to demonstrate graphically the effect of certain topically administered drugs on the blood vessels of the iris. The size of certain blood vessels, which were injected with India ink, has been measured in rats with miosis or mydriasis.

Materials and Methods

Adult hooded and albino rats were given ether anesthesia about one-half hour after topical administration to their eyes of 5% homatropine hydrobromide or 0.1% isoflurophate (diisopropyl fluorophosphate). The abdomen was opened widely, and the lower thorax was entered through the diaphragm to expose the lower thoracic and upper abdominal aorta. A glass cannula was inserted in a cephalad direction into the aorta just below the diaphragmatic attachment and held in place by a firm ligature. The animal was allowed to bleed to death through the open end of the cannula. Then the rat was injected through the cannula with an India ink-plasma mixture at 4 lb. pressure. Almost immediately the ink appeared in the iris, tongue, and forefeet of the animal. The cannula was removed; the aorta was ligated, and the entire animal was placed in 10% formalin solution for 24 hours. Then the eyes were opened coronally near the ora serrata. In animals with pigment the anterior segment was bleached with 3% potassium permanganate and 2% oxalic acid. The iris and ciliary body were separated in one piece from the cornea and mounted flat on a slide in glycerin jelly, covered with a cover glass, and sealed.

The diameter of the blood vessels was measured with a calibrated ocular micrometer. In each iris-ciliary body preparation the diameter of the major circle and radial iris vessels was measured in microns. Each major circle was measured in four places, that is, halfway between the origin and termination of each of the four branches of the two long posterior ciliary arteries. The caliber of a radial iris vessel was measured in each of these four segments at a point opposite to the point of major circle measurement and approximately halfway

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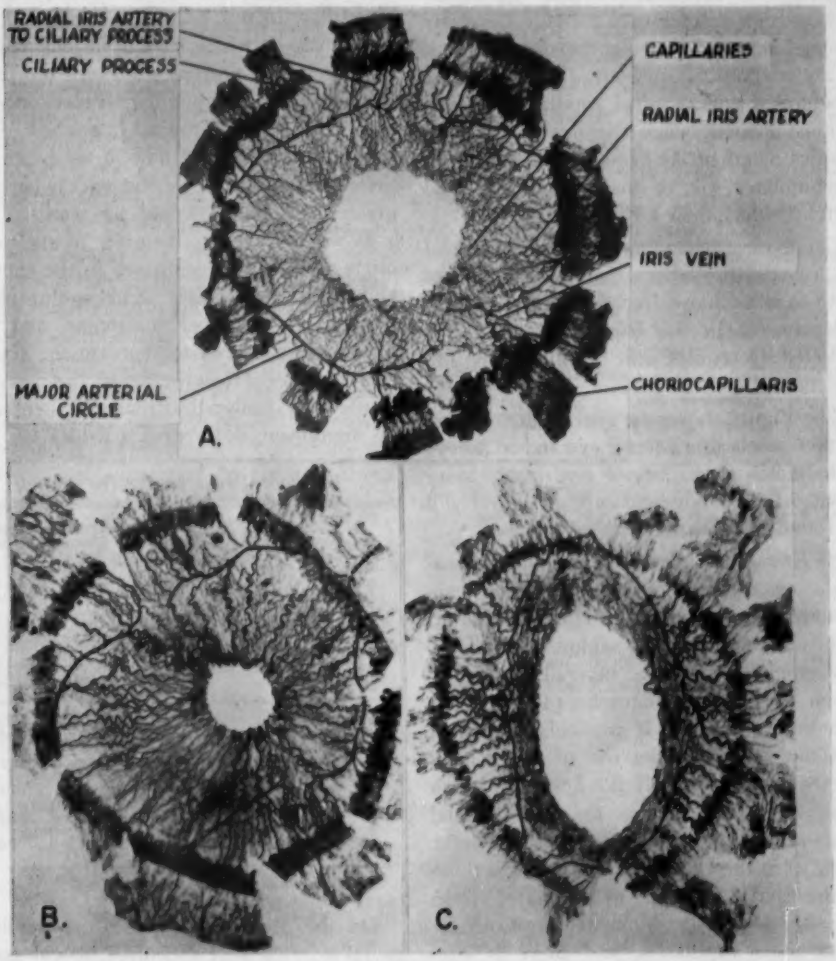
along its length to the pupillary margin. The surface area of the pupil was measured in square millimeters with a planimeter.

Results

A. Anatomy of the Iris Vasculature.—The blood vessels of the rat iris differ somewhat from those of the human being as far as their origin and distribution are concerned.

Most of the blood reaches the iris and ciliary body by way of two long posterior ciliary arteries. After reaching the ciliary body these vessels divide dichotomously, and the resultant four branches form the major arterial circle. These two nasal and two



Whole mounts of irises and ciliary bodies injected with India ink. *A*, control, showing rather uniform filling of all blood vessels. The blackness of the ciliary body is caused partly by India ink and partly by incomplete bleaching. Pupillary area 4.91 sq. mm. *B*, miosis produced with isoflurophate. Capillaries near ciliary body are not so completely filled, and the radial iris vessels have a greater diameter than those of the control. Pupillary area 1.34 sq. mm. *C*, mydriasis produced with homatropine. Pupil was originally round but was distorted in preparing whole mount. Note that the constriction of the iris tissue occurs chiefly on the pupillary side of the major arterial circle and that the radial iris arteries have a greater diameter than those of the control. Pupillary area 7.36 sq. mm.

temporal branches of the circle enter the iris from above and below, and they are generally terminal vessels, i. e., they do not anastomose. Anterior ciliary arteries per se are not seen in the rat, although small twigs may come into the ciliary body from the conjunctiva.

Small radial arteries or arterioles branch from the major circle at rather regular intervals, some extending to the pupillary margin and others supplying the outer portion of the iris and ciliary body. These iris vessels have a typical coiled appearance, which is most evident when the pupil is dilated. Miotics lengthen the vessels, particularly on the pupillary side of the major circle, and thereby reduce their tortuosity.

Capillaries arise from the coiled radial iris vessels throughout their length. These seem to anastomose freely and form a dense vascular net in the iris tissue. Blood is collected by venules which drain chiefly into the choroid.

The Figure shows the general distribution of the vessels in a control eye and in an eye with miosis and one with mydriasis. More details of the iris vasculature of the rat will be found in an earlier paper.[6]

B. Effect of Homatropin and Isoflurophate on the Iris Vessels.—Isoflurophate produced a marked constriction of the rat pupil within a very few minutes. Likewise, homatropine caused a marked dilatation. When the photomicrographs (Figure) are examined grossly, it is particularly evident that the vessels in the iris of the control rat are more uniformly filled with ink than those in rats receiving the experimental drugs. Actually the greatest difference in the filling is in the capillaries, particularly those on the ciliary body side of the major circle. No attempt has been made to measure or count these capillaries, and there is considerable variation from one eye to another. However, those shown in the figures are typical. One interesting point is that the tissue that contracts or expands during the dilatation or constriction of the pupil is chiefly on the pupillary side of the major circle and the capillary distribution is more constant in this region, in all three specimens. It is true that all capillaries in a particular structure are not patent at one time and would not be expected to fill with India ink, but the fact that the peripheral ones show reduced filling in both the miotic and the mydriatic eyes might indicate that the topically applied drugs were altering the blood flow in this particular area.

The vessels which have been of particular interest in the present study are the major circle arteries and pupillary radial ones. It was felt that if topically applied drugs should alter the blood flow in the irises that these vessels would be the ones where the greatest alteration would be seen.

When the average diameter of the major circle arteries was compared in the controls and the homatropine- and isoflurophate-treated eyes, both homatropine and isoflurophate appeared to increase the size of these vessels. However, when the measurements were analyzed statistically there were no significant differences (Table).

Effect of Drugs on the Iris Vessels

	Measurements, No.	Average Diameter, μ	Standard Deviation
Controls			
Radial	88	16.1	± 4.6
Major circle	88	53.6	±14.8
Homatropine-treated			
Radial	64	20.7	± 6.4
Major circle	64	56.6	±12.2
Isoflurophate-treated			
Radial	60	23.3	± 9.1
Major circle	60	56.6	±16.8

Comparisons	t* Value
1. Control radial with homatropine radial	4.90
2. Control radial with isoflurophate radial	5.37
3. Homatropine radial with isoflurophate radial	1.67
4. Control major circle with homatropine major circle	1.37
5. Control major circle with isoflurophate major circle	1.12
6. Homatropine major circle with isoflurophate major circle	0.00

*Significantly different when greater than 3.0.

On the other hand, when the pupillary radial arteries were measured, it was found that they had a larger diameter in both the isoflurophate- and the homatropine-treated rats than in the controls.

The mechanism whereby isoflurophate causes the dilatation of certain blood vessels seems to be clearly understood. Isofluro-

phate inactivates cholinesterase, either by destroying it or by irreversibly combining with it.[7] The resulting accumulation of acetylcholine in the iris would then override the action of the sympathetic nerve influence on the arteries. This would permit these vessels to dilate in response to intravascular pressure.

On the other hand, the action of homatropine in causing the radial iris vessels to enlarge is more difficult to explain. This drug apparently acts by occluding the receptor surface in the muscle so that acetylcholine cannot act on the muscle fibers. Thus, one would expect these vessels to be constricted. However, their increase in diameter may be accounted for by the fact that not only do these vessels spiral during the constriction of the iris but there is also a linear shortening. This would account for their apparent dilatation after topically applied homatropine.

Thus, the congestion of the iris vessels following the topical administration of homatropine would not be caused by the pharmacologic dilatation of the blood vessels per se but by the condensation of tissue during the dilatation of the pupil.

Summary

The blood vessels of the iris were studied after topical administration of homatropine or isoflurophate (DFP).

The major circle arteries in the different series of animals were the same size, but homatropine- as well as isoflurophate-treated eyes had radial iris vessels of a greater diameter than controls.

The enlargement of these vessels in the isoflurophate-treated animals may be explained by the pharmacological action of this drug. The greater size in the homatropine-treated animals may be accounted for by the linear contraction of the vessel, which is concomitant with the dilatation of the pupil.

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The Bony Orbital Walls in Horizontal Strabismus

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In the fundamental quest of etiology in nonaccommodative and nonparalytic horizontal strabismus, recent electromyographic (EMG) or electro-oculographic (EOG) studies have begun to separate—with a new index of reliability—the so-called innervational squints from those of possibly mechanical origin. Scobee's extensive works emphasized the etiologic role of structural anomalies in the check ligaments, muscle insertions, and other soft tissues of the orbit. Neither students of strabismus nor pure orbital anatomists, however, have extensively analyzed the angulations of the bony orbital walls in relation to the position of the globes.

The purposes of this study are (1) to establish normal radiographic values for the angulations of the orbital walls in orthophoric persons of different sex, age, and race and (2) to analyze such bony orbital angles in relation to various horizontal imbalances. Accommodative, paralytic, and vertical heterotropias are excluded.

Background

The classical studies of orbital angles are those of Felix Lagrange (1903), Emil Emmert (1880), Merkel (1901), and Adachi (1904). Whitnall,[1] in 1921, and Duke-Elder,[2] as late as 1932, still drew on these measurements of dried skulls for descriptions of the orbital angles. Goldnamer,[3] in 1923, reported measurements on 41 skulls selected at random from the Anthropological Department of the Field Museum of Natural Science in Chicago. Emmert, studying 25 skulls, described the angle between the external orbital walls as 87.4 degrees in children 10 to 17 years of age; 89.9 degrees in males aged 20 to 67 years, and the same in women 23 to 67 years of age. Lagrange found this angle to vary from 87.4 to 90.6 degrees; the angle between the lateral and medial walls was found to vary from 45.9 to 48.6 degrees. Merkel, studying 20 skulls, noted that the medial orbital walls were parallel in only 11% of cases and that generally the medial walls diverged by about 3 mm. from the orbital apex to the anterior rim.

All of these osteologic measurements were made without regard to antemortem muscle balance.

Method of Present Study

A radiographic technique was selected for this study in order to correlate bony anatomy with orthophoric and heterophoric states in the living patient. A special submentovertex view (Fig. 1) was utilized, with the patient's shoulders lying on a pillow and the head fully extended. This usually produced satisfactory delineation of the orbital walls as visualized in horizontal section, but occasionally the mandible obscured the apex and such films had to be discarded.

Strabismus patients were selected from the strabismus clinic of the University of Louisville through the courtesy of Dr. Charles T. Moran, director of this clinic. The angle of deviation for near and for distance was recorded at the time of x-ray study. A short history was transcribed, noting age, race, sex, type of anomaly, time of onset, hereditary factors, and previous treatment.

Control patients without motility problems were selected from the general eye clinics of the University of Louisville after preliminary ophthalmic examination and cover

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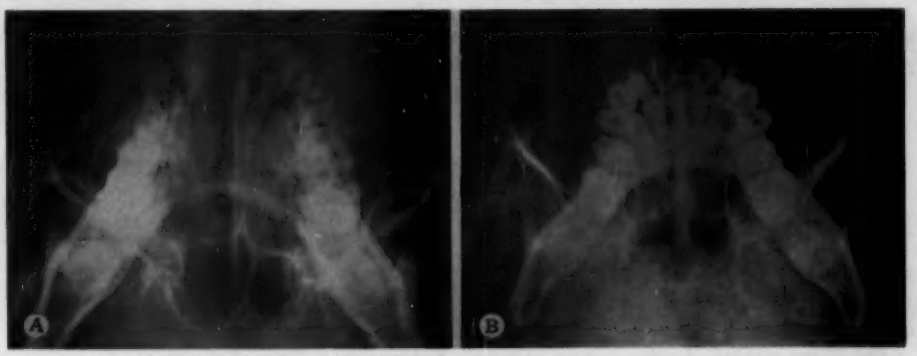

Fig. 1.—Submentovertex roentgenograms used for measurement of orbital angles. *A*, Negro orthophoric control patient; *B*, white orthophoric control patient.

test for near and for distance to rule out heterophoria.

From the x-ray films, direct tracings were made of the medial and lateral orbital walls, and the lines of the lateral walls were projected backward to measure their relationship. Each angle was measured with a protractor, and the relations of the medial orbital walls were noted as (*a*) parallel, (*b*) divergent anteriorly, or (*c*) convergent anteriorly.

Angles were noted as follows (Fig. 2):

Angle 1 (right and left), the angle between the medial and lateral orbital walls on the designated side.

Angle 2 (right and left), the angle between the medial sagittal line and the lateral wall of the orbit on the designated side.

Angle 3, the angle formed by projecting posteriorly the lateral walls of each orbit.

Satisfactory roentgenograms were obtained on 134 patients divided into the following groups:

White control	40
White esotropic	33
White exotropic	11
Negro control	28
Negro esotropic	12
Negro exotropic	10

Findings

The incidence of medial versus lateral deviations was markedly different in the white and Negro patients of our clinic. Among the 44 white patients with purely horizontal strabismus, the ratio of exotropia to esotropia was 1:3; among the 22 Negro patients, the ratio was 5:6.

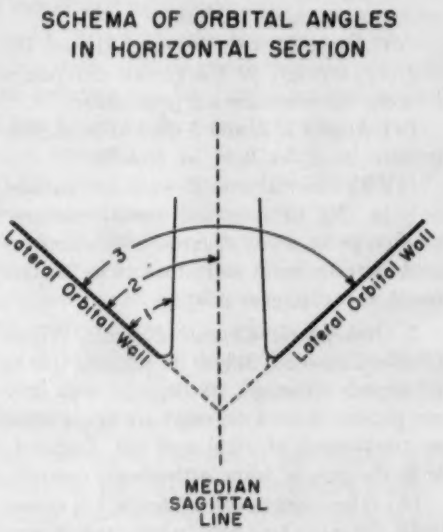

Figure 2

Each of the six groups of patients was further broken down into (*a*) patients below 12 years of age and (*b*) patients above 12 years of age. These subgroups were then divided into males and females. Data are grouped in the six Tables according to these divisions. Figures are arithmetic means for the numbers of cases as indicated.

1. *Orthophoric Control Patients, White* (Table 1).—(*a*) Right and left Angles 1

TABLE 1.—*Orthophoric Control Patients (White) (Forty Cases)*

Age, Yr.	Sex	Cases, No.	Angle 1, Degrees		Angle 2, Degrees		Angle 3, Degrees	Medial Walls		
			Rt.	Lt.	Rt.	Lt.		Parallel	Conv.	Div.
0-12	M	13	49.6	50.8	49.2	47.9	97	1	9	3
	F	12	48.8	49.2	47.5	48.3	95.7	2	5	5
12-33	M	4	49.8	49.8	47	47.5	94.5	1	3	
	F	11	48.9	48.8	47.2	46.7	93.4	1	8	2

are generally unequal by 0 to 7 degrees (average, 1.4 degrees, only one case above 3 degrees).

(*b*) Right and left Angles 2 show slightly greater range of inequality (vary from 0 to 8 degrees; average, 2.2 degrees, with seven cases above 3 degrees).

(*c*) Angle 3 varies between 81 and 107 degrees (average, 95.3 degrees); differences between the sexes are not pronounced.

(*d*) Angles 1, 2, and 3 tend to be slightly greater in males than in females.

(*e*) The medial orbital walls are parallel only in 12% of cases and usually converge or diverge by a few degrees, with a convergent relation being more than twice as frequent as a divergent relation.

2. *Orthophoric Control Patients, Negro* (Table 2).—(*a*) Slight inequalities (0 to 10 degrees; average, 1.8 degrees, with only one patient above 4 degrees) are again noted on comparison of right and left Angles 1, as in the case of white orthophoric controls.

(*b*) The average size of Angle 1 is essentially the same in both white and Negro orthophoric control patients below the age of 12 years; above this age, the Negro group shows Angle 1 values about 2 degrees larger than the white group.

(*c*) Right and left Angles 2 tend to be slightly larger than those of the white orthophoric control patients, and inequalities between right and left run slightly higher (0 to 9 degrees; average, 3.1 degrees, with five patients above 4 degrees).

(*d*) Angle 3 varies between 88 and 120 degrees (average, 98 degrees), with the large figures again confined to persons above the age of 12 (where they exceed Angle 3 values of orthophoric white controls by amounts up to 5 degrees).

(*e*) Angles 1, 2, and 3 tend to be somewhat larger in males than in females, and this sex difference is particularly pronounced in Angles 3.

(*f*) Relations of medial orbital walls to each other are approximately the same as in white orthophoric control patients.

3. *Esotropic Patients, White* (Table 3).—(*a*) In monocular esotropia (30 cases) Angle 1 is generally smaller on the side of the deviating eye by amounts up to 8 degrees, but in two cases, or 7% of these esotropes, this angle was found to be larger (average, 4 degrees) on the side of the esotropic eye; in seven cases (or 23%) Angles 1 were found to be equal.

(*b*) In monocular esotropia, Angle 2 tends to be slightly smaller on the side of the deviating eye, but such inequalities are less marked than in Angle 1, and in eight cases (25% of cases) the angle was larger on

TABLE 2.—*Orthophoric Control Patients (Negro) (Twenty-Eight Cases)*

Age, Yr.	Sex	Cases, No.	Angle 1, Degrees		Angle 2, Degrees		Angle 3, Degrees	Medial Walls		
			Rt.	Lt.	Rt.	Lt.		Parallel	Conv.	Div.
0-12	M	13	50.2	50.4	50	50.8	98.6	2	6	5
	F	8	48.7	48.5	48.4	46.1	93.8	1	6	1
12-26	M	3	51	52.7	49.7	50.7	99.3		2	1
	F	4	51	50	48.5	49.5	96.8	1	3	

TABLE 3.—*Esotropic Patients (White) (Thirty-Three Cases)*

Age, Yr.	Sex	Cases, No.	Type of Dev.	Angle 1, Degrees Rt.	Angle 1, Degrees Lt.	Angle 2, Degrees Rt.	Angle 2, Degrees Lt.	Angle 3, Degrees	Medial Walls Parallel	Medial Walls Conv.	Medial Walls Div.
0-12	M	16	Rt. (0) Lt. (8) Alt. (2)	49.4 45	47 45	47.1 47.5	46.1 46	92.6 93.5	2	4 1	2 1
	F	16	Rt. (6) Lt. (7) Alt. (3)	47.3 49.3 49	51.2 47.9 47	50.6 49.1 48.3	49.5 49.3 50.7	99.5 97.9 97.3	4	3 1 1	3 2 2
12-26	M	4	Rt. (4) Lt. (0) Alt. (0)	48.3	50.3	47.8	49.5	97.3		2	2
	F	3	Rt. (2) Lt. (1) Alt. (0)	47.5 50	49 45	45.5 50	48 50	93 100	1	1	1

the side of the esotropic eye by amounts up to 8 degrees.

(*c*) Angle 3 varies between 80 and 106 degrees (average, 96.3 degrees), which is essentially the same range as seen in the white orthophoric control cases.

(*d*) In alternating esotropia (four cases) Angles 1 are equal or show slight inequalities (average, 1 degree; range 0 to 3 degrees) within the range found in the orthophoric control group, but Angles 2 show wider variability (average, 8 degrees; range, 1 to 13 degrees).

(*e*) Relations of the medial walls to each other are similar to those of the orthophoric control group except that the frequency of divergence and convergence are found to be equal.

4. *Esotropic Patients, Negro* (Table 4). —(*a*) In monocular esotropia (six cases) Angle 1 is generally smaller on the side of the deviating eye than the side of the non-deviating eye by amounts up to 21 degrees, but in two cases this angle was found to be larger on the side of the esotropic eye (5 degrees and 9 degrees); in one case Angles 1 were found to be equal.

(*b*) In monocular esotropia, Angle 2 tends to be slightly smaller on the side of the deviating eye, but in two patients Angle 2 was larger on the side of the esotropic eye by 2 degrees.

(*c*) Angle 3 varies between 82 and 112 degrees (average, 99 degrees).

(*d*) In alternating esotropia (six cases) Angles 1 and also Angles 2 are equal or fall within the small range of inequality found in the orthophoric control group.

(*e*) Relations of the medial walls to each other are the same as in white esotropic patients.

5. *Exotropic Patients, White* (Table 5.) —(*a*) In monocular exotropia (nine cases) Angles 1 are generally larger on the side of the deviating eye by amounts up to 7 degrees (average, 4 degrees); in no case was this angle found to be smaller on the side of the

TABLE 4.—*Esotropic Patients (Negro) (Twelve Cases)*

Age, Yr.	Sex	Cases, No.	Type of Dev.	Angle 1, Degrees Rt.	Angle 1, Degrees Lt.	Angle 2, Degrees Rt.	Angle 2, Degrees Lt.	Angle 3, Degrees	Medial Walls Parallel	Medial Walls Conv.	Medial Walls Div.
0-12	M	6	Rt. (2) Lt. (1) Alt. (3)	47.5 50 47.7	47.5 49 47.7	47 50 47.3	49.5 47 48	95 97 94	1 1	1 1	1 1
	F	4	Rt. (1) Lt. (0) Alt. (3)	55 48.3	55 51	52 52	50 55	102 104.3		1 1	2
12-16	M	2	Rt. (0) Lt. (2) Alt. (0)	56.5	43	55	46.5	101		1	1
	F	0	Rt. Lt. Alt.								

TABLE 5.—*Exotropic Patients (White) (Eleven Cases)*

Age, Yr.	Sex	Cases, No.	Type of Dev.	Angle 1, Degrees		Angle 2, Degrees		Angle 3, Degrees	Medial Walls		
				Rt.	Lt.	Rt.	Lt.		Parallel	Conv.	Div.
0–12	M	2	Rt. (0)								
			Lt. (1)	45	47	46	54	98			1
			Alt. (1)	48	50	46	50	96			1
	F	1	Rt. (0)								
			Lt. (1)	47	47	50	52	102			1
			Alt. (0)								
12–18.5	M	2	Rt. (1)	54	52	44	50	94		1	
			Lt. (1)	48	52	50	50	105			1
			Alt. (0)								
	F	6	Rt. (1)	47	49	57	45	100			1
			Lt. (5)	47.4	51.4	45.2	51.2	96.8		3	2
			Alt. (0)								

exotropic eye, and in only one case were the Angles 1 found to be equal.

(*b*) In monocular exotropia, Angle 2 tends to be greater on the side of the deviating eye by amounts up to 12 degrees (average, 5 degrees), but in one patient the angle was 6 degrees smaller on the side of the exotropic eye.

(*c*) Angle 3 varies between 82 and 105 degrees (average, 98 degrees).

(*d*) Alternating exotropia is represented by only one patient in this group, and therefore generalizations cannot be made.

(*e*) Relations of the medial orbital walls show divergence twice as frequently as convergence, which is the reverse of the relation found in the orthophoric control patients.

6. *Exotropic Patients, Negro* (Table 6).—(*a*) In monocular exotropia, Angle 1 is generally larger on the side of the deviating eye by amounts up to 11 degrees (average, 6 degrees); in no case was this angle found to be smaller on the side of the exotropic eye and in only one case were the Angles 1 found to be equal.

(*b*) In monocular exotropia, Angle 2 tends to be greater on the side of the exotropic eye by amounts up to 6 degrees (average, 3 degrees), but in 50% of cases Angles 2 are equal.

(*c*) Angle 3 varies between 85 and 107 degrees (average, 97 degrees).

(*d*) In alternating exotropia, Angles 1 and also Angles 2 show only slight inequalities falling within the range seen in the Negro orthophoric control group.

(*e*) Relations of the medial orbital walls are essentially the same as in the esotropic patients, with the frequency of divergence and convergence being essentially equal.

Summary

Submentovertex roentgenograms were made to define the relationships of the bony orbital walls in horizontal section in 68 orthophoric control patients (age 3 to 33 years) and in 66 patients with purely horizontal, nonaccommodative, and apparently nonparalytic strabismus (age 8 months to 25 years).

TABLE 6.—*Exotropic Patients (Negro) (Ten Cases)*

Age, Yr.	Sex	Cases, No.	Type of Dev.	Angle 1, Degrees		Angle 2, Degrees		Angle 3, Degrees	Medial Walls		
				Rt.	Lt.	Rt.	Lt.		Parallel	Conv.	Div.
0–12	M	1	Rt. (0)								
			Lt. (1)	46	57	51	54	103			1
			Alt. (0)								
	F	5	Rt. (0)								
			Lt. (3)	48	51.3	40	52.3	101		1	2
			Alt. (2)	50	51	49.5	50.5	100	1	1	
12–20	M	1	Rt. (0)								
			Lt. (1)	47	58	43	43	86		1	
			Alt. (0)								
	F	3	Rt. (0)								
			Lt. (1)	47	50	50	50	100			1
			Alt. (2)	48	50	45.5	46.5	90.5		2	

A. Orthophoric Control Patients. — 1. Right and left Angles 1 are equal in 60% of the white subjects and 50% of the Negro (average, 55%). The remaining control cases show inequalities averaging about 1.5 degrees, with only two subjects above 3 degrees.

2. Angle 1 values are essentially the same in white and Negro patients below the age of 12, but above this age Negro patients show values a few degrees larger than those of white patients.

3. Statistical values for Angles 2 are slightly higher and considerably less consistent than those for Angles 1.

4. Angles 1, 2, and 3 tend to be slightly larger in males than in females.

5. Angle 3 values averaged 95 degrees (range, 81 to 107 degrees) in the whites and 98 degrees (range, 88 to 120 degrees) in the Negroes, with the larger values in the older Negro males.

6. Medial orbital walls are parallel in 12% of cases and usually converge or diverge by a few degrees, with anteriorly convergent relations being more than twice as frequent as anteriorly divergent relations.

B. Esotropic Patients, Negro and White. —1. In monocular esotropic patients, Angle 1 values are equal in only 22% of cases (compared with 55% in control cases) and Angle 1 is smaller on the side of the esotropic eye in 67% of cases. In 25% of monocular esotropes a "significantly" smaller (4 to 21 degrees) Angle 1 is found on the side of the deviating eye.

2. In alternating esotropia, Angles 1 are equal in 50% of cases, and in the remaining cases they fall within the slight range of inequality found in the orthophoric control group.

3. No significance is attached to the relationship of the medial orbital walls.

C. Exotropic Patients, Negro and White. —1. In monocular exotropic patients, Angles 1 are equal in only 13% of cases (compared with 55% in control cases) and Angle 1 is larger on the side of the deviation in the remaining 87% of cases. In 33% of monocular exotropes a "significantly" larger (4 to 11 degrees) Angle 1 is found on the side of the deviating eye. In no case of monocular exotropia was Angle 1 found to be smaller on the side of the deviating eye.

2. In alternating exotropia, insufficient cases are available for generalization, but only one case showed inequality of right and left Angle 1, beyond the average of the control series.

3. No significance is attached to the relationship of the medial orbital walls.

Conclusions

The angle formed by the medial and lateral wall of each orbit (designated Angle 1) is equal on the right and left side in 55% of the orthophoric patients studied; in the remainder there are slight inequalities which average about 1.5 degree and range below 10 degrees.

Twenty-five per cent of monocular esotropic patients show significantly smaller Angle 1 values (differing by amounts up to 21 degrees) on the side of the deviating eye. No significant inequalities are found between right and left Angles 1 in alternating esotropic patients of this series.

Thirty-three per cent of monocular exotropic patients show significantly larger Angle 1 values (differing by amounts up to 11 degrees) on the side of the deviating eye.

As part of the routine evaluation of patients with nonaccommodative and nonparalytic horizontal muscle imbalance, a routine submentovertex x-ray should be taken from which the right and left orbital angles may be measured. Twenty to thirty-five per cent of such patients with monocular deviations may be expected to have significant inequality between the right and left bony orbital walls, associated with the direction of deviation. Where such structural irregularities exist, corrective surgery may be better

undertaken at an early rather than a more mature age, and as a monocular rather than a binocular procedure. Conversely, where the bony orbital angles are found to be equal, as in the alternating patients presented, the use of symmetrical or bilateral surgery would seem to be better supported.

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The Effect of Certain Drugs on Corneal Impedance

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Introduction

The extraordinary capacity of the mammalian cornea to become hydrated has been recognized for many years. Leber recorded the phenomenon in 1873 and further noted that hydration led to opacity. Aurell and Holmgren (1953) have quantitated this characteristic of corneal tissue and have found that an excised cornea in water may swell as much as 13 times its normal volume, whereas a scleral segment under equivalent treatment cannot increase its volume more than threefold. The fact that an excised cornea will swell even when immersed in tears or aqueous humor, the fluids which normally bathe it, raises the question as to what the living, intact tissue does to prevent its continual hydration.

A number of suggestions have been made to explain this peculiarity of corneal tissue and the mechanisms which govern it in life. Woodin (1950) proposes that the corneal mucoitin polysaccharide may account for the capacity to take in water, and Hart and Chandler (1948) believe that the geometry of the corneal "gel" is the key to the degree of imbibition. Working with intact as well as excised membranes, Cogan and Kinsey (1942) proposed their theory of dehydration based on an asmotic gradient, suggesting that fluid entering at the limbus is withdrawn osmotically across the limiting surfaces by the hypertonic tears and aqueous humor. The solutes, thus stranded, presumably establish a back equilibrium with the limbal capillaries. Later studies by Potts and his group (1950, 1953, 1954) and Maurice (1951, 1955), with tracer ions, demonstrated the permeability of both the epithelium and the endothelium to salts and even suggested (Potts, 1953) that sodium may be actively transported across the posterior membrane.

One of the many unusual aspects of the corneal epithelium is its enormous content of acetylcholine (von Brücke, 1938, 1949). In view of the ability of this neurohumor to depolarize cell membranes, it was thought that it might affect permeability in the corneal epithelium as well. The purpose of this work was thus to investigate the corneal acetylcholine from the point of view of tissue hydration. Various drugs known to affect acetylcholine metabolism were placed on the tissue, and any changes in corneal permeability, as measured by the impedance of the tissue to an alternating current, were noted.

It will be seen that the drugs elicited but few effects.

Materials and Methods

Fresh cattle eyes were used. The cornea was excised immediately and placed in a simple plastic clamp. Mammalian Ringer-Locke solution was made up according to Pantin (1946). The pH was kept at 7.2± 0.2 by saturation with CO_2 and subsequent, minimal, buffering. The total molarity of this combined salt solution was 0.15 M. Straight Ringer solution and Ringer solution of twice this molarity were made up regularly. The double Ringer solution was subsequently diluted 3:1 with distilled water to yield a bathing solution half again as concentrated as the normal Ringer solution. To simulate the aqueous humor, the inside surface of the cornea was bathed in the straight Ringer fluid (0.15 M); to approximate the tears, made hypertonic by evaporation, the more concentrated Ringer solution (0.234 M) was used against the

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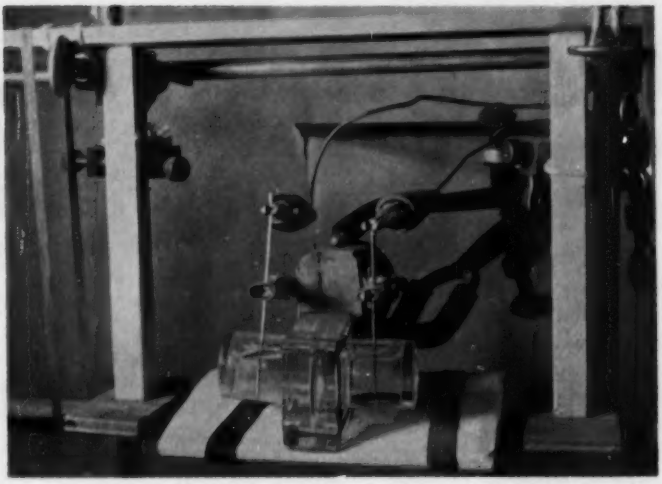


Fig. 1.—Apparatus for measuring corneal impedance, with clamp and cornea in place. The lower, depressible platform is held in place by large rubber bands. The wires lead to the "unknown" terminals of the Z-angle meter. Clamp measures 7 cm. across.

epithelial surface. Unless a gradient was put across the tissue in this manner, the impedance values never attained a satisfactory equilibrium.

A silver electrode, held stationary, was placed on either side of the tissue (Fig. 1). The current source was a Hewlitt Audio Oscillator, Model 200B. It was set at 1000 cps, with an amplitude value of 30 throughout. The impedance bridge was a Technical Instrument Corporation Z-Angle Meter, Type 310, which registered total impedance in ohms and the phase angle in degrees. It was also possible to determine whether the reactance was capacitative or inductive. Because of the nature of the meter, the total voltage impressed across the system was held constant at 0.04 volts. All runs were made at room temperature.

The bathing solutions were left untouched until an equilibrium had been reached. A cornea was considered to be in a state of stability from the point of view of impedance when at least three-quarters of an hour could pass with a change of impedance value of no more than 10 ohms in either direction. The average reading was about 1200 ohms, with a phase angle (capacitative) of 27 degrees. The fluid bathing the epithelial side was replaced by the drug solution, and subsequent readings were taken to quantitate the effects. Since all corneas showed very nearly the same pattern of impedance change, most of the graphs are drawn on the basis of the direction and amount of this change rather than on the basis of the absolute readings.

The drugs were chosen for their known actions on the acetylcholine or other neurohumoral systems. They were pilocarpine hydrochloride, neostigmine (Prostigmine), physostigmine, tetraethylpyrophosphate (TEPP), atropine sulfate, and epinephrine. Without exception, they were made up in 0.234 M Ringer's solution, the fluid they replaced.

Observations and Data

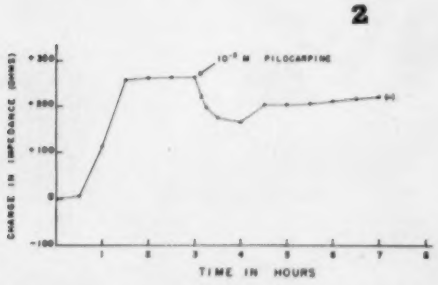
It was evident that the impedance measurements were, in fact, correlated with the hydration of the tissue. Inevitably, a decrease in impedance was accompanied by hydration and opacity, whereas an increased value was evidence for dehydration and, actually, a clarification of the tissue. Furthermore, it was evident that these impedance properties resided solely in the epithelium. The stroma, stripped of its overlying layer, showed but negligible impedance, regardless of its own state of hydration, as Holt and Cogan (1946) have previously shown.

Various tonicities of salts were placed against the tissue, and a consistent pattern

was seen: As long as the outer surface was bathed by fluid hypertonic to the inside bathing solution, some dehydration took place and the impedance values rose, the speed and degree of increase varying proportionately with the steepness of the osmotic gradient. With no salt gradient, the impedance value dropped in parallel with a very obvious hydration.

Use of the standard Ringer solution, 0.156 M against the inside and 0.234 M against the epithelium, also elicited a uniform pattern. There was a gradual rise in impedance value, undoubtedly accompanying a slight dehydration by the hypertonic salt solution, until finally a plateau in electrical readings gave evidence of an established equilibrium. Only after this level had been reached were the drugs applied.

No drugs elicited a further increase in impedance, though a few of them brought about a decreased impedance value. Pilocarpine, 10^{-3} M, caused a drop in impedance of nearly 100 ohms, indicating a small increase in permeability (Fig. 2). Cocaine, of equivalent molarity, likewise effected a drop in impedance, of approximately 50 ohms (Fig. 3). TEPP, 1:10^6, elicited a 40 ohm drop (Fig. 4), though neither neostigmine nor physostigmine at 10^{-3} M concentration caused a significant change. A concentration of 10^{-3} M of epinephrine caused no impedance changes. Finally, atropine was tried in several concentrations. In the strength of 10^{-3} M or less, no appreciable change in impedance value was noted. Ten per cent atropine, however, caused first a steep increase in impedance and then a steady de-



Figs. 2, 3, and 4.—Effect of certain drugs on corneal impedance. The number in the parenthesis indicates the number of corneas used for testing the effect of each drug. These were equilibrated with 0.156 M mammalian Ringer-Locke solution bathing the inside and 0.234 M Ringer solution bathing the epithelial side. After the plateau had been established, the outside solution was replaced with the drug of the strength indicated. Control eyes, whose outside solution was replaced with fresh 0.234 M Ringer solution, showed no significant change of impedance during the experimental period.

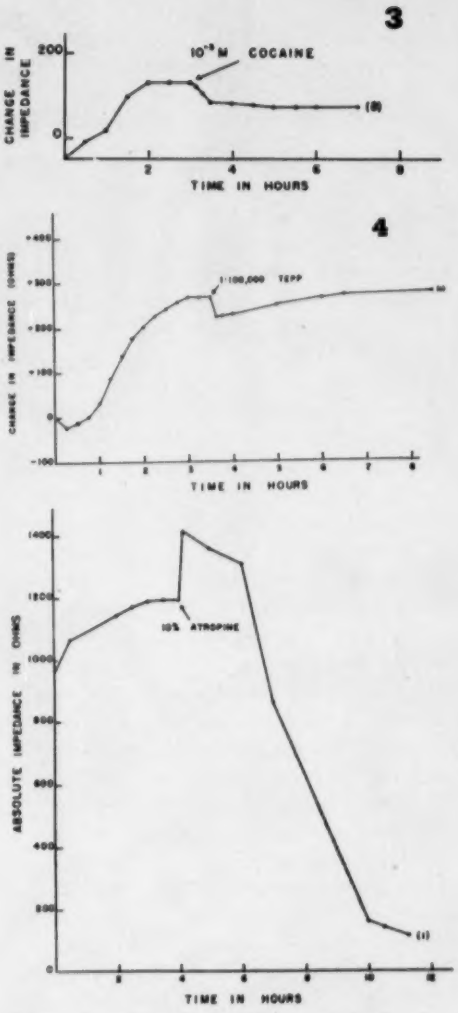


Fig. 5.—Changes in the value of absolute impedance of a single fresh cornea with 10% atropine against the epithelial surface. This cornea was treated identically with the other experimental eyes.

crease (Fig. 5). It was evident from the appearance of the tissue that actual damage had occurred to the epithelium.

Comment and Conclusions

Clinical evidence suggests that most if not all of these drugs penetrate corneal tissue, and thus any difference of action between them cannot be discounted merely as a function of material entry. TEPP was the only anticholinesterase tried which had any effect on hydration, for neither physostigmine nor neostigmine elicited a change. The lipid insolubility of TEPP makes its unique action among the group all the more surprising. Philpot (1955) also worked with anticholinesterases and corneal hydration, using as her criterion the weight increase of excised portions. She, too, found that 10^{-3} M neostigmine elicited no significant change in the hydration rate of rabbit corneas, but she showed that 8.2×10^{-4} M isoflurophate caused a slight increase.

It will be recalled that 10^{-3} M pilocarpine also caused a slight hydration. The similar effects of this acetylcholine mimic, pilocarpine, and the anticholinesterase, TEPP, suggest that free acetylcholine may serve in part to increase the permeability of the tissue to salts and water. If this were strictly true, then one might expect atropine to effect an increase in impedance representing a decreased permeability. Holt and Cogan (1946) found that a 10% solution of atropine sulfate in 0.9% NaCl caused a prompt increase in impedance to 50% more than the original reading, a constant effect (lasting 20 hours) which could be quickly reversed. In this work, with the salt gradient across the tissue, these results could not be repeated. In this case, the 10% atropine solution was made up in 0.234 M Ringer's solution, and after an initial rise in the impedance value there was an irreversible decline. Under these conditions, it seems likely that the immediate increase is due to osmotic effects and the latter depression is the result of actual damage to the tissue. Use of the drug in concentrations of 10^{-3} M (here) or 1.7×10^{-3} M (Philpot, 1955) resulted in no effect on hydration.

The hydrating action of cocaine, on the other hand, has been noted by several investigators. In studying epithelial regeneration, Swan (1949) found that cocaine increased the permeability, and Ullerich and Durchschlag (1953) further reported that cocaine hampered epithelial regrowth. Holt and Cogan (1946), however, found that a 4% solution of cocaine hydrochloride in 0.9% NaCl elicited a 65% increase in impedance, a value which, like that with 10% atropine, was stable and reversible. It seems possible that this effect might, again, be partly an osmotic one. It will be recalled that the experimental results in the present study indicate a slight hydrating action by the drug in concentrations of 10^{-3} M.

In conclusion, it may be said that, with use of impedance measurements as a test of permeability, the drugs which normally act on or through the acetylcholine system had but slight effects on the degree of corneal hydration and permeability. One may tentatively conclude that the high amounts of acetylcholine in the epithelium have little to do with the water metabolism of corneal tissue.

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Radioiodine Content of Aqueous, Vitreous, and Lens

An Experimental Study in Rabbits

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Introduction

Radioiodine is one of the important entities in the diagnosis and treatment of thyroid conditions. Greater numbers of patients are receiving increasing amounts of radioiodine. In the treatment of functioning carcinoma of the thyroid the doses of radioiodine being used are large and are steadily being made larger. This study of the penetration of radioiodine to the aqueous, vitreous, and lens of rabbits was undertaken to determine the probability of significant corneal and lenticular damage resulting from the intrinsic radiation inherent in treatment doses of radioiodine.

Methods and Material

Eleven rabbits, five white albino and six brown Flemish giants, weighing between 2.1 and 3.25 kg. were given approximately 4.5 mc. (millicuries) of I^{131}. On the basis of millicuries per kilogram body weight, this approximates the dose which is presently being used in our isotope unit for the treatment of thyroid cancer.

Four of the rabbits were not in a fasting state; the other seven were fasting. The doses were all administered through a short Levin tube to the stomach.

At intervals from 15 minutes to 43 hours, with use of intravenously administered pentobarbital anesthesia, aqueous, vitreous, and lens were examined for radioactivity. Aqueous was collected by anterior chamber puncture through the cornea with a No. 26 hypodermic needle attached to a micropipette. The vitreous was removed by means of aspiration with an ordinary syringe and No. 18 needle through the equator of the globe. The lens was expressed. The lenses were washed in tap water or isotonic saline, without preference, by running the wash fluid into the test tube containing the the lens, shaking three times, draining off the fluid, and repeating 20 times. This was done so that the activity of the lens itself, or at least lens plus very intimately bound material which would have to be considered in lens radiation, could be determined.

The blood of one rabbit was sampled at intervals from 4 minutes to 28 hours for determination of blood levels of radioiodine for comparison with the ocular radioiodine levels.

The effect of paracentesis of the anterior chamber on the I^{131} levels in aqueous, vitreous, and lens was also determined.

The counting of all radioactivity was done in a scintillation well counter.

Results and Comment

Following the administration of radioiodine to the stomachs of the rabbits, the aqueous showed a gradual rise in I^{131} counts, with peak levels being reached between 14 and 20 hours. After this there was a slow falling off of the radioactivity until very low levels were reached, at 43 hours (Fig. 1). Vitreous and lens showed the same general type of curve, with the peak counts being attained in vitreous be-

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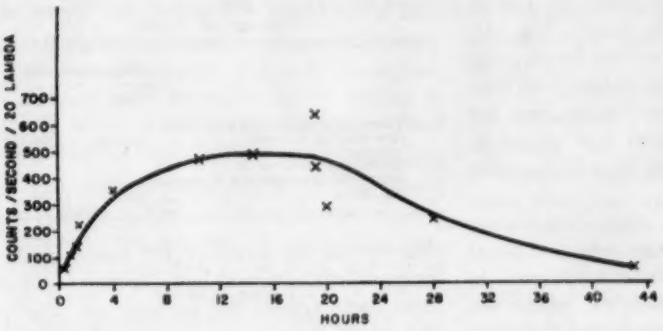

Fig. 1.—I^{131} count of the aqueous of rabbit following absorption from the gastrointestinal tract.

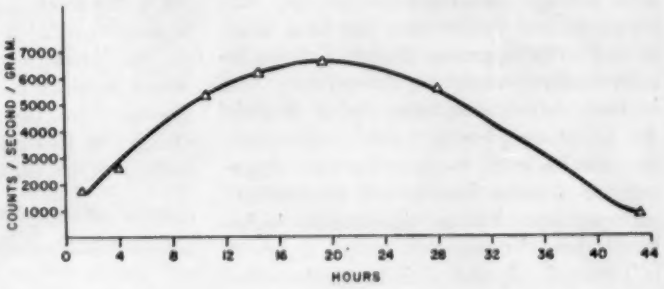

Fig. 2.—I^{131} count of the vitreous of rabbit following absorption from the gastrointestinal tract.

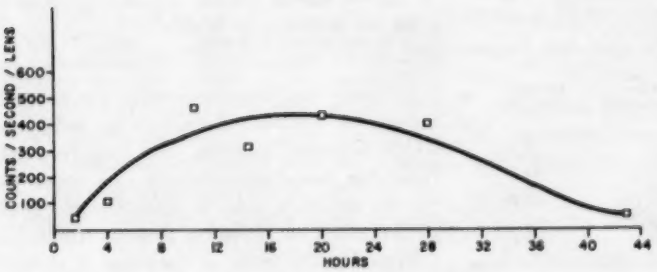

Fig. 3.—I^{131} count of the lens of rabbit following absorption from the gastrointestinal tract.

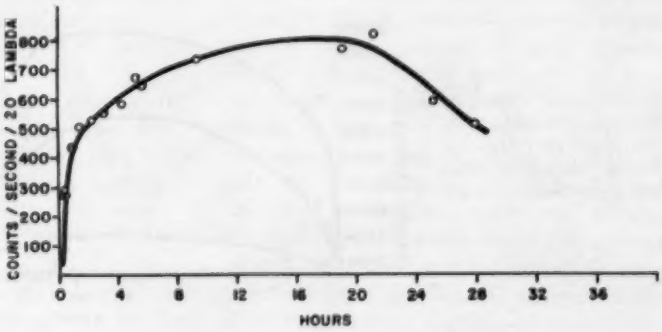

Fig. 4.—I^{131} count of blood of rabbit following absorption from the gastrointestinal tract.

tween 16 and 22 hours (Fig. 2) and in lens between 15 and 21 hours (Fig. 3). The radioiodine levels in the blood were found to show a slightly faster rise than those in the aqueous, vitreous, or lens, but otherwise the same general type of curve, with peak counts between 15 and 21 hours, was recorded (Fig. 4).

In an effort to get more comparative values for aqueous, vitreous, lens, and blood a plot was made of these substances in terms of the common unit of counts per second per gram. We assume that the aqueous had a specific gravity of 1; blood, 1.050. The average measured lens weight was 0.46 gm., and the vitreous had been measured directly in grams. Figure 5 shows the comparative values so determined, with highest radioiodine counts being reported for blood and lowest (and comparatively very small) levels recorded for lens. Aqueous and vitreous counts were intermediate, with aqueous having significantly higher levels than vitreous.

Tables 1, 2, and 3 indicate the effect produced by paracentesis of the anterior chamber on the levels of I^{131} found in the aqueous, vitreous, and lens. It may be seen from these figures that paracentesis rapidly and significantly increases the I^{131} concentration. We feel that this is consistent with the well-known change in character of the aqueous produced with paracentesis—that is, the production of plasmoid aqueous, which becomes more and more like blood plasma. One can then speculate that the changes in lens and vitreous would be secondary to the change in aqueous.

TABLE 1.—*Effect of Paracentesis on I^{131} Count of Aqueous of Rabbit*

Eye	Minutes After Administration of I^{131}	Counts/Sec./20λ
1. Operated on	22	54
Same eye	42	443
Same eye	77	464
Untraumatized	48	104
Untraumatized	75	153.95
2. Operated on	48	104
Operated on, same eye	93	648.6

TABLE 2.—*Effect of Paracentesis on I^{131} Count of Vitreous of Rabbit*

	Counts/Sec./Gm.	
	Left	Right
1. Left eye operated on at 22 min.; both eyes removed at 90 min.	2,339.69	1,890.72
2. Right eye operated on at 19 hr. 15 min.; both eyes removed at 19 hr. 19 min.	6,615	11,182

TABLE 3.—*Effect of Paracentesis on I^{131} Count of Lens of Rabbit*

	Counts/Sec.	
	Left	Right
1. Right eye operated on at 15 min.; both eyes removed at 52 min.	101.42	161.42
2. Left eye operated on at 22 min.; both eyes removed at 90 min.	192.3	91.8

Utilizing our experimentally determined curves, we determined the average radiation which aqueous, vitreous, and lens received from the doses administered. In order to err on the high side, it was assumed that all the effective radiation present would be delivered to the tissue in question. It should

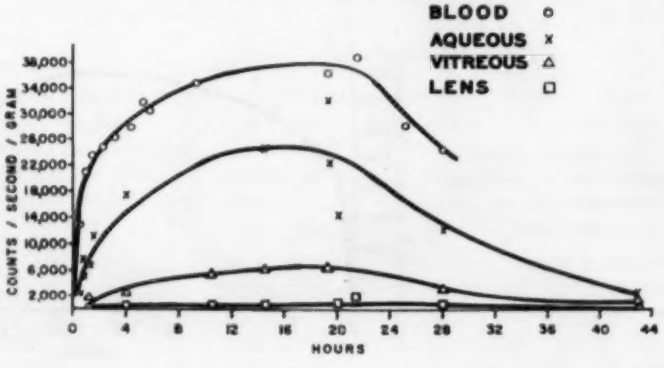

Fig. 5.—I^{131} count of aqueous, vitreous, lens, and blood of rabbit following absorption from the gastrointestinal tract.

be noted that while I^{131} has both a beta and a gamma emission it is only the β-rays, with poor penetrance and with consequent absorption and ionization in the tissues at hand, which concern us. The contribution of the highly penetrating γ-ray is negligible.

The radiation dosages were determined as follows: The radiation dosage rate is related to the amount of radioactive material per gram and the average energy of the β-ray by the equation $I=2.13\ AE$. I is the number of rads per hour (1 rad equals 100 ergs per gram of tissue); A is the number of microcuries (μc) per gram of tissue, and E is the average energy of the β-ray in million electron volts (mev). The average energy of the β-ray of I^{131} is 0.189 mev.[1]

The procedure followed to obtain the average number of microcuries per gram is illustrated here with the calculation for the aqueous. For the first 40 hours the average counting rate of the aqueous, determined by the use of a planimeter on the graph, was 318 counts per second per 20 λ (lambda). This is equivalent to

$$\frac{318}{20\lambda}\left(\frac{1000\lambda}{\text{ml.}}\right)=15{,}500 \text{ counts per second per ml.}$$

The efficiency of our scintillation well counter for I^{131} is 50%—i. e., one-half of the disintegrations occurring result in a count being recorded. There are 37,000 disintegrations per second in 1 mc.; hence the average concentration of I^{131} in the aqueous which has a density equal to unity is

$$\frac{(15{,}500)\,(2)}{(37{,}000)}=0.84\mu\text{c per gram}$$

Therefore the average radiation intensity is

$$(2.13)\,(0.84)\,(0.189)=0.34 \text{ rads per hour}$$

and the total dose for the first 40 hours is 13.6 rads.

For vitreous the average counting rate was 4690 counts per second per gram, which leads to an average concentration of 0.254μc per gram, an average radiation activity of

$$(2.13)\,(0.254)\,(0.189)=0.102 \text{ rads per hour}$$

and a total dose of 4.08 rads for the first 40 hours.

The lenses had an average weight of 0.46 gm. and an average counting rate per lens of 594 counts per second. This results in a concentration of 0.0349μc per gram, an intensity of

$$(2.13)\,(0.0349)\,(0.189)=0.014 \text{ rads per hour}$$

and a total dose of 0.56 rads for the first 40 hours.

Thus the radiation received by the structures concerned was as follows:

Aqueous	13.6 rads
Vitreous	4.08 rads
Lens	0.56 rads

Because the units of measurement of radiation have been changing,[2] we feel that definitions of present terms are pertinent here and will make the above figures more easily comparable to other writings in the literature. The number of ergs (unit of energy) absorbed per gram of tissue when exposed to one roentgen (r) of x- or γ-rays varies with the composition of the tissue and the energy of the particular ray involved. In the usual situation in therapy, 1 r results in approximately 93 ergs absorbed per gram of tissue.

One roentgen equivalent physical (1 rep) equals 93 ergs absorbed per gram of tissue.

The new unit, the rad (radiation absorbed dose), which is used in this report, equals 100 ergs absorbed per gram of tissue.

Thus one can see that the various units of radiation presently used approximate each other reasonably closely.

Conclusions

Reference to the literature reveals both experimentally and clinically that doses far in excess of those we determined are needed before significant damage to normal cornea and lens may be expected. Cogan[3] reports that 600 to 1000 r is necessary for lens opacity and that 2000 to 4000 r may be used on the cornea therapeutically. Merriam[4] recommends surface eye doses of 2000 to 3000 rep. Von Sallmann and Dillon[5] noted that with intraperitoneal I^{131} and autoradiographs approximately twice the amount of I^{131} was taken up in the cornea as compared with the aqueous. Thus, even if one doubled or tripled our experimentally de-

rived figures the amount delivered would still not result in damage. Gurney et al.[6] have determined in humans that insufficient I^{131} to produce corneal damage is found in human tears after cancerocidal doses. Kandori[7] reports the minimal cataractogenic level in rabbits to be 900 r.

Thus it may be concluded that, even with cancerocidal dosage of I^{131}, penetrance of sufficient radiation to the eye to produce lens or corneal damage is highly unlikely.

Summary

The penetrance of radioactive iodine from the gastrointestinal tract to the aqueous, vitreous, and lens of rabbits has been studied.

Effect of paracentesis on I^{131} content in aqueous, vitreous, and lens of rabbits is noted.

It is felt that significant cornea and lens damage resulting from the intrinsic radiation inherent in cancer treatment doses of radioiodine is unlikely.

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Blue Sclerotics with Fragilitas Ossium and Deafness

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Blue sclerotics is a congenital anomaly characterized by a uniform light-blue coloration of the sclera. It is congenital and hereditary and is usually associated with other abnormalities, such as multiple fractures, dislocation of joints, laxity of ligaments, and deafness (van der Hoeve's syndrome). The condition was first described by Adair-Dighton (1912), but van der Hoeve and de Kleyn (1918) were the first to include deafness definitely with this congenital anomaly, and the symptom-complex is accordingly often known as van der Hoeve's syndrome.

Blue Sclerotic

It is generally accepted that the unusual appearance of the sclera is due to its abnormal translucency. The color, which is usually evident at birth, does not change throughout life. The color is, however, darker in the anterior part of the sclera, over the ciliary body. In the absence of a sufficient number of microscopic examinations of the sclera in this syndrome, any dogmatic opinion regarding the anatomical basis of this translucency is inadvisable. Conflicting views have been expressed by Buchanan (1903, 1923) and Bronson (1917). Buchanan found scleral fibers of normal size but unusually thin. Casanovas (1934) confirmed Buchanan's findings. Bronson, however, found no abnormality in thickness, and the size and number of fibers were normal. The cause of this abnormal translucency—whether a quantitative or a qualitative defect—is not yet settled.

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Fragilitas Ossium

Fragilitas ossium is a rare congenital condition characterized by unusual brittleness of the bones, which are, therefore, likely to undergo fractures either spontaneously or on trivial injuries. It may form part of a syndrome involving blue sclerae, hypermobility of joints, and otosclerosis.

The following types of fragilitas ossium are recognized: 1. Osteogenesis imperfecta (Vrolik's disease, osteopsathyrosis congenita) (Looser, 1906), in which fractures occur in utero, skull changes are usually present, and early death is the rule. Both parents usually have normal bones and sclerae. 2. Osteopsathyrosis tarda (Looser, 1906), in which first fractures occur after birth, usually in childhood; the sclerae may or may not be blue, and both parents have normal bones and sclerae. It is familial but not hereditary. Cases with blue sclerae may show all the characteristics of Group 3. 3. Brittle bones and blue sclerae. In this group the first fractures occur in childhood and the sclerae are always blue. One parent always has blue sclerae, with or without the bone affection. The condition is hereditary and may be traced as a Mendelian dominant. The fractures tend to become less frequent after puberty, when otosclerosis often appears.

Though the association of abnormal fragility of bones with blue sclerae was noted early by Eddowes (1900) and Spurway (1896), proper attention was not focussed on this association running in families until a much later date. The fractures sustained by the patients of this category have certain peculiarities—they give rise to less pain than usual; union is not delayed, although

it is frequently imperfect and fibrous. This tendency to fractures decreases with advancing age.

Pathologic Physiology and Chemistry

The tendency for the bones to undergo fractures either spontaneously or on trivial injuries is best explained by their inability to form proper bone matrix. The serum calcium and phosphorus in these cases are found within normal limits. The serum alkaline phosphatase may be slightly elevated, suggesting that the basic defect is not a paucity of osteoblasts but rather their inability to produce adequate matrix.

Dislocations and subluxations occur owing to weakness of the capsular ligaments (Behr, 1913).

Deafness

Van der Hoeve and de Kleyn (1918) were the first to associate deafness with blue sclerotics and brittle bones. It usually appears after the age of 20 and gradually progresses and eventually affects 60% of subjects (Dessoff, 1934). The deafness is usually bilateral. It is generally thought that deafness is due to otosclerosis, but it has been also thought to be due to labyrinthine diseases or to abnormal thinness of the tympanic membrane and laxity of the ligaments attached to the ear ossicles (Dessoff).

Heredity

The condition has a definite hereditary and familial tendency. The transmission is of a simple dominant type. Occasionally the condition occurs in a person with normal ancestors, which suggests either a recessive inheritance or a new mutational origin. In some pedigrees blue sclerotics is always linked with fragility of bones or otosclerosis or both, while in others the association is less close (Key, 1926). It has been estimated that 60% of persons with blue sclerotics have fragilitas ossium, 60% have otosclerosis, and 44% have all the three defects. It seems likely that the three defects are germinally independent but genetically linked. Key (1926) has remarked that fragile bones or blue sclerae occurring singly or together in a patient with no similar cases in the family cannot be regarded as a case of the syndrome under consideration. Bell (1928) considers scleral anomaly as the dominant characteristic in this syndrome. Among families with complete van der Hoeve syndrome the incidence of this condition in subsequent generations can be predicted by Mendelian law. When one parent is affected, the disease may be anticipated in 50% of the children, and when both parents are affected, in 75% of the children. It never skips a generation.

Other Associated Abnormalities

Key is of opinion that usually the syndrome is observed in persons who do not exhibit other defects. Duke-Elder (1943) included references in which were described keratoconus, embryotoxon, megalocornea, zonular cataract, macular atrophy of skin, late development of teeth, retrobulbar neuritis, cleft palate, spina bifida, congenital heart disease, and hemophilia. A general deficiency of stature is the rule.

Etiology

The etiology of this syndrome is still obscure. The condition is undoubtedly due to some developmental error in the mesenchymal tissue, the underlying cause of which is still a matter of speculation. The endocrine glands that have been suspected are thyroid, thymus, pituitary, and, more recently, parathyroids. Dessoff (1934) suggested hyperparathyroidism as a possible cause. Rados and Rosenberg (1936) have reviewed the possibility of endocrine disturbance underlying this syndrome, and they are of opinion that there have not been found sufficient variations in the values of calcium, phosphorus, and phosphatase to warrant such a supposition. Luzzatto

(1949) is of opinion that this wide-spread developmental aberration of the mesenchymal system is due to collagen disease.

Treatment

Dr. Marian Ropes believes that positive calcium balance can be attained with both estrogens and androgens in patients suffering from this disorder and that these persons are benefited by this type of therapy.

Report of Cases

CASE 1.—A 46-year-old Hindu woman came to the outpatient department of N. R. Sircar Hospital, Calcutta, complaining of headache and pain in the eyes and defective vision on Nov. 2, 1955. On examination it was found that she had blue sclerae; otherwise, externally there was no abnormality. Vision was 6/6 each eye. She accepted a correction of $+0.25 \bigcirc +0.25$ axis 90 degrees. Fundus oculi was healthy.

She had had fractures of the lower end of the humerus of both arms in childhood on very trivial injury (while playing with some girls she was caught by the hand, and she sustained fractures). The fractures healed uneventfully. She had been suffering from gradual and progressive defective hearing for the last six years. On examination it was found that she had definite otosclerosis in both ears. The hearing test revealed marked loss of air conduction (over 80 db.) but no loss in bone conduction, which showed rather an apparent increase.

Other abnormalities: The patient had flat feet and valgus deformity of the feet; stature was short.

Biochemical estimation of blood: glucose, 64 mg. per 100 ml.; Na, 133.0 mEq. per liter; K, 57 mEq. per liter; Ca, 5.0 mEq. per liter; serum alkaline phosphatase, 5.5 units per 100 ml. (King-Armstrong method); serum acid phosphatase, 1.75 units per 100 ml. (K. A. method); ascorbic acid, 1.3 mg. per 100 ml.

Urinary excretion in 24 hours: Na, 188 mg. per 100 ml.; K, 77.5 mg. per 100 ml.; Ca, 6.3 mg. per 100 ml.

CASE 2.—An 18-year-old Hindu woman, the youngest daughter of Case 1, was found to have blue sclerae. There was a history of fracture of the lower end of the left humerus six years back, following a very trivial injury (slight jerk by the hand while playing). Hearing was normal. Vision: R. E. 6/9 with +0.5 D. cyl axis 90 degrees = 6/6; L. E. 6/6 ?? with +0.5 D. cyl axis 90 degrees = 6/6. Fundus oculi healthy.

Other abnormalities: flat feet, eversion of ankle, valgus deformity of feet, both arches of feet dropped; stature, short.

Biochemical estimation of blood: glucose, 70 mg. per 100 ml.; Na, 162.6 mEq. per liter; K, 7.7 mEq. per liter; Ca, 5.2 mEq. per liter; serum alkaline phosphatase, 7 units per 100 ml.; serum acid phosphatase, 2.25 units per 100 ml.; ascorbic acid, 1.6 mg. per 100 ml.

Urinary excretion in 24 hours: Na, 285 mg. per 100 ml.; K, 59.5 mg. per 100 ml.; Ca, 6.5 mg. per 100 ml.

CASE 3.—A 23-year-old Hindu woman, the second daughter of Case 1, had blue sclerae ++. There was a history of fracture lower end of right humerus 11 years back (nature of trauma could not be ascertained). Hearing, normal. Vision each eye, 6/6 with +0.5 D. cyl axis 90 degrees = 6/6. Fundus oculi healthy.

Other abnormalities: varus deformity of the feet; stature, stunted.

Biochemical estimation of blood: glucose, 61 mg. per 100 ml.; Na, 138.3 mEq. per liter; K, 5.4 mEq. per liter; Ca, 3.7 mEq. per liter; serum alkaline phosphatase, 6 units per 100 ml.; serum acid phosphatase, 3 units per 100 ml.; ascorbic acid, 1.1 mg. per 100 ml.

Urinary excretion in 24 hours: Na, 235 mg. per 100 ml.; K, 45.8 mg. per 100 ml.; Ca, 6.3 mg. per 100 ml.

CASE 4.—A 38-year-old Hindu man, brother of Case 1, had blue sclerae ++

*Results of Study of Blood in Four Cases of Blue Sclerotics**

	Na, mEq. /L.	K, mEq. /L.	Ca, mEq. /L.	Glucose, Mg. /100 Ml.	Serum Alkaline Phosphatase, Units/100 Ml.	Serum Acid Phosphatase, Units/100 Ml.	Serum Ascorbic Acid, Mg./100 Ml.
Case 1	133.0	5.7	5.0	64	5.5	1.75	1.3
Case 2	162.6	7.7	5.2	70	7.0	2.25	1.6
Case 3	138.3	5.4	3.7	61	6	3	1.1
Case 4	131.3	5.1	4.1	52	8.5	2.8	0.9

* In all the cases glucose was found to be below the normal level. There was no increase in the serum alkaline phosphatase. There was slight elevation of serum potassium level in all the cases and also slight elevation of serum ascorbic acid.

and had had deafness + for four years. There had been fracture of the right humerus 22 years previously and fracture of the left humerus 31 years previously. Vision: right eye 6/9 and with +0.75 D. cyl axis 90 degrees=6/6. Left eye 6/9 and with +0.5 D. cyl axis 90 degrees=6/6. Fundus oculi healthy, both eyes.

Other abnormalities: eversion of ankle; bilateral flat feet, more marked in left; valgus deformity of both feet, more marked in left; dropping of both arches of feet; feet, longish and slender type; height, stunted.

Biochemical estimation of blood: glucose 52 mg. per 100 ml.; Na, 131.3 mEq. per liter; K, 5.1 mEq. per liter; Ca, 4.1 mEq. per liter; serum alkaline phosphatase, 8.5 units per 100 ml.; serum acid phosphatase, 2.8 units per 100 ml.; ascorbic acid, 0.9 mg. per 100 ml.

Urinary excretion in 24 hours: Na, 346 mg. per 100 ml.; K, 53.5 mg. per 100 ml.; Ca, 5.1 mg. per 100 ml.

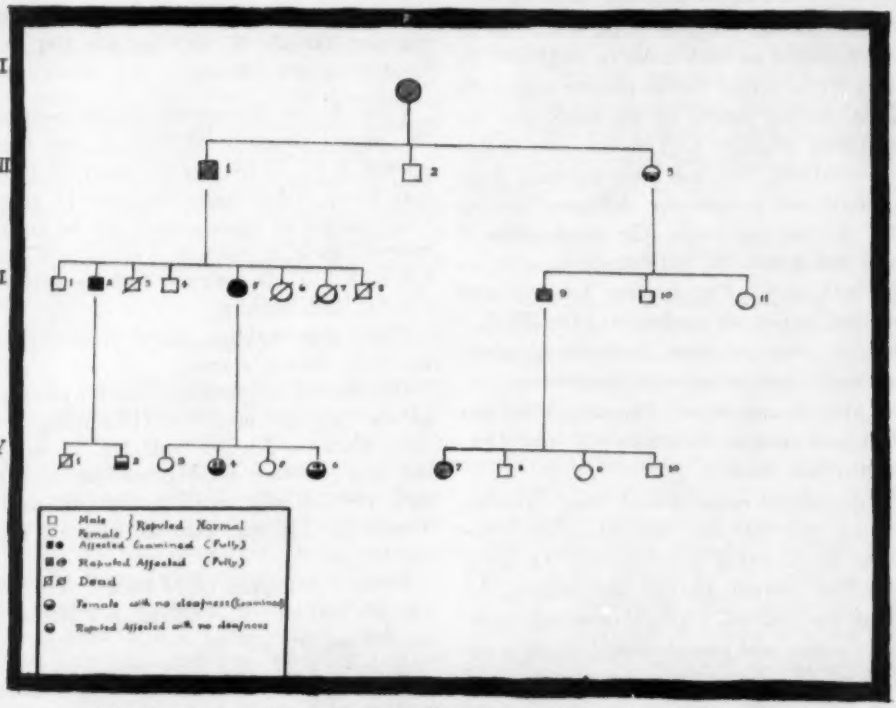

Fig. 1.—Van der Hoeve syndrome. Pedigree showing dominant inheritance.

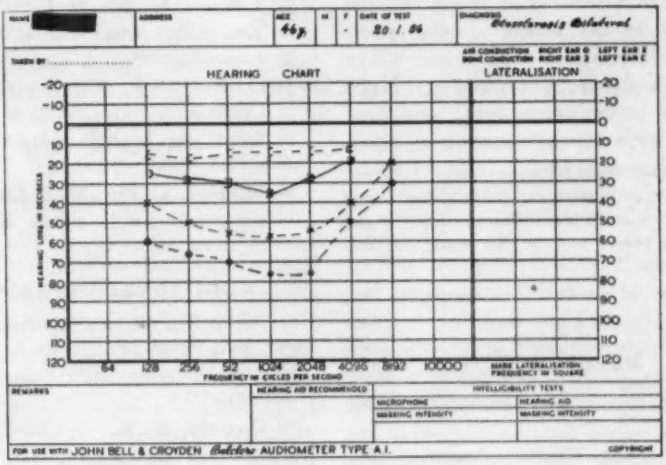

Figure 2 (Case 1)

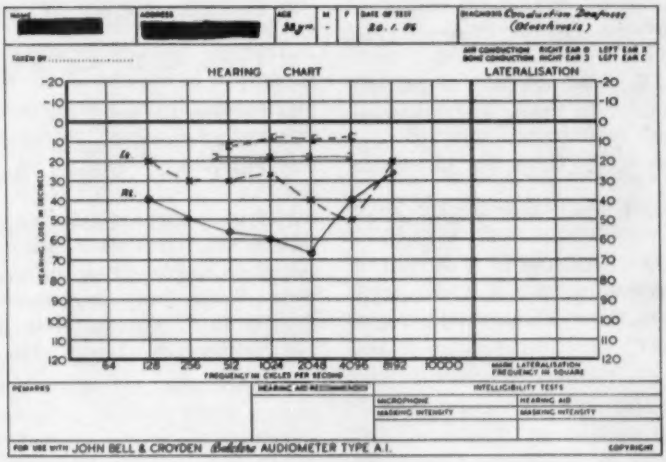

Figure 3 (Case 4)

The defect in hearing is due to a mild degree of otosclerosis in the right ear. In the left ear hearing is normal.

The biochemical estimation of blood of the above four cases is summarized in the accompanying Table.

The family tree of the cases is given in Figure 1. The pedigree shows definite dominant inheritance. The audiometric curves of Cases 1 and 4 are given in Figures 2 and 3.

Summary

A family of van der Hoeve's syndrome traced through four generations with reports of four cases is presented. The pedigree definitely shows a dominant inheritance.

All four cases sustained fractures in the upper limbs before puberty. Two of the cases (Cases 1 and 4) developed slowly progressive defects in hearing after the age of 35, the cause of which is found to be due to otosclerosis. All the cases presented here have some defects in the feet.

Biochemical estimation of blood revealed no increase in the serum alkaline phosphatase level. Glucose was found to be below the normal level in all cases. Slight elevation of serum potassium level and serum ascorbic acid was found in all cases.

The Superintendent, Nilratan Sircar Hospital, Calcutta, gave permission to publish the cases; Dr. N. Banerjee made the audiogram reports, and Drs. B. Chakrabarty and S. Sen made the biochemical reports.

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Eye Disorders Associated with Surgical Problems of the Nervous System

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It is my intention to limit this discussion to those eye disorders having problems which require diagnostic screening or treatment by a neurosurgeon. The ophthalmologist admittedly is the clearing agent for the general recognition of a large group of eye abnormalities which he is especially trained to detect. However, he often reaches a point in diagnosis or therapy where his common knowledge and experience makes it obvious that he should seek the help of some other specialist who can supplement his efforts. With the advance in mechanical sciences there has been rapid progress in the development of mechanical diagnostic methods for the precise recognition of deep lying, formerly poorly understood, intricate gross lesions of the cranial cavity which cripple the ocular machinery. By the injection of air into the fluid-bearing spaces of the spine and skull and contrast media, thorium dioxide (Thorotrast) and iodopyracet (Diodrast), into the cerebral vessels we can now visualize by roentgen photography the complete detailed gross texture of the brain and its vessels. Iophendylate (Pantopaque) provides the same diagnostic visualization for lesions of the spinal cord and spine. Electrocephalography and various types of electrical energy are now of great value in the diagnostic clarification and treatment of neurological disease. These and many other very recently developed diagnostic methods are essential for furnishing valuable information on which to base specific therapy. However, they are safe and of value only when carried out with cautious precision and unusual skill by persons thoroughly trained in the execution of these maneuvers. Paralleling the increasing accuracy of the new diagnostic methods has been improvement in the surgical procedures for correcting mechanical defects. There has been no greater or more rapid advance in the surgical sciences than in the specialty of neurological surgery, and particularly in that part related to visual disorders.

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Sensory Disorders of the Eye

Probably the most striking example of a minor disturbance in sensation about the eye is the corneal anesthesia or hypesthesia caused by a tumor in the cerebellopontile angle. These tumors are commonly neurofibromas growing from the vestibular portion of the auditory nerve. Their first and only subjective symptom for a long period is slowly progressive unilateral deafness. This is usually recognizable at the time the patient first consults the ophthalmologist for mild headache and numbness about the eye. A careful stroking of the cornea with a wisp of cotton will disclose corneal anesthesia or marked hypesthesia even before sensory changes can be detected in other parts of the face. Very often there is no edema of the discs or nystagmus at this stage of the growth. If these tumors are suspected at this stage by these two or three symptoms, a positive diagnosis with successful removal of the tumor is possible and a permanent cure can be accomplished.

The sharp, paroxysmal, stabbing pains of tic douloureux (trigeminal tic) may localize just above or below the eye but seldom directly in the globe or orbit. Characteristically it can be identified by long periods of absence of the pain (days, weeks, or months), its aggravation or initiation by stroking the eye lids or brow, and the fact that it seldom affects the other side of the face or changes its pattern of distribution. There is no specific efficacious medical treatment, and it does not leave spontaneously. Formerly this pain could be stopped permanently only by a major brain operation which removed the Gasserian ganglion or sectioned the sensory root of the trigeminal nerve or by the hazardous procedure of destroying the ganglion by the injection of alcohol into it. Three years ago I discovered and perfected the method of permanently controlling the pain by injecting the ganglion with boiling water under x-ray visualization and light anesthesia.[1] In my first group of more than 100 patients so injected, for the pain of tic douloureux and cancer of the face, there has not been a single seriously ill person, facial paralysis, or corneal complication. Six per cent had temporary extraocular weakness affecting either the third, fourth, or sixth nerves, with double vision. All recovered completely in less than five months. All have had adequate moisture of the cornea, with a complete return of emotional and physiologic lacrimation on regeneration of the autonomic nerve fibers to the lacrimal gland, in three to five months. In a recent critical review of 250 tic douloureux patients treated by this method and by intracranial sensory root section, this method has been found to be far superior to any other past treatment for the permanent cure of this disorder.

Aneurysm of the extradural carotid canal at the base of the skull causes sharp, piercing pains located in the globe and eye socket. It may be indistinguishable from tic douloureux without arteriography. Since these are gross gradually expanding dilations within the cavernous sinus at a point where they lie very near the ophthalmic division of the trigeminal, fourth, and sixth nerves, there is often corneal and supraorbital hypalgesia and double vision. Rupture of this aneurysm produces a fistula between the carotid and cavernous sinus with a resulting progressive pulsating exophthalmos. Simple aneurysm of the carotid canal can be cured by trapping it between a ligature of the carotid in the neck and one inside the cranial cavity through a craniotomy opening. The risk is not great providing the aneurysm is not too immense and the patient can withstand carotid ligation. If the aneurysm has ruptured and produced a fistula with pulsating exophthalmos it can be cured only by the double ligation as described and the plugging of the fistulous opening with an embolus of muscle floated into it through an opening in the carotid in the neck. By this method I have permanently cured 10 patients.

Aneurysms of the intracranial carotid just as it enters the intradural cranial cavity are often referred to as "berry," "supraclinoid," or "third nerve" aneurysms. They are the size of a small raspberry, pedunculated, and located between the clinoid process and posterior communicating artery. The onset of symptoms is usually sudden and often attended with shock caused by the sudden expansion or rupture of the aneurysm. Frontal and orbital headache which spreads to the back of the neck is the first symptom. Third nerve paralysis, with its turned-out eyeball, ptosed lid, and dilated pupil, is a telltale sign that is pathognomonic. The third nerve palsy often comes on a few days to a week or more after the onset of headache. However, without third nerve involvement one can still be certain of this lesion by arteriography. Arteriography will usually clearly visualize the aneurysm.

The modern treatment for this lesion is elimination by ligation of the aneurysm stem via craniotomy. This operation is attended by a relatively low mortality as compared with the risk of not ligating it or of ligating the carotid in the neck. The hazard of this procedure is not in its surgical approach but from possible inadequacy of the cerebral circulation, should it be necessary

to ligate the carotid in continuity in the neck or at the site of the origin of the aneurysm. The risk involved can be predicted with considerable accuracy by the age of the patient, the arteriographic pattern of the aneurysm, and the condition of the cerebral vessels. In June, 1949, I reported on the ligation of these aneurysms by craniotomy in 20 patients, with a mortality of 25%.[2] Many more have been since operated on, with a resulting gradual reduction in operative mortality. Following operation the third nerve usually regenerates, with a complete restoration of binocular vision. There have been no deaths in the surviving group from aneurysm rupture. Death from a second hemorrhage occurs too often to warrant nonoperative treatment of this lesion.

Herpes zoster ophthalmica is a lesion which is probably seen in greater numbers by the neurosurgeon than by any other specialist. In fact, the problem of trigeminal herpes in its acute and chronic states is a common one in our practice. More than 90% of all patients with tic douloureux treated by inspection or operation develop herpes eruption on the face as a result of traumatic activation of the dormant herpes virus around the Gasserian ganglion. Fortunately these lesions are almost always inside the cheek or lips and on the skin surface of the upper and lower lips. This type only rarely affects the cornea and spontaneously heals without residual pain or scarring.

When corneal herpes occurs concomitantly with facial paralysis and corneal anesthesia it is apt to be malignant and devastating. Penetrating ulcers of the cornea may occur in 24 hours with panophthalmitis, and, should the eye be saved, an opaque corneal scar directly over the pupil may render vision hopeless.

How, then, does the neurosurgeon cope with this constant problem which always threatens vision? At the first indication of conjunctival irritation which has herpes as its probable cause, we strictly refrain from "patching" the eye. Instead, a moist chamber, made from x-ray film, is tightly sealed over the eye by means of soft zinc oxide or flexible plastic adhesive. We never use cellophane or "waterproof" tape for this purpose, since it is too stiff to fit smoothly and tightly. Next, the patient's room is kept very warm and humid, with the doors closed and water boiling constantly on a hot plate. Wide-spectrum antibiotics are given, and fluids by mouth and vein are forced. An antiseptic ointment (ophthalmic boric) is placed on the lids, and no emphasis is placed on the direct application of cleaning agents or local antiseptics to the lesion itself. The eye shield is lifted and the external surfaces of the lids are cleaned with moist cotton to remove exudate, making certain that nothing but the under surface of the lids touches the cornea.

Should the irritation be more serious and a definite abrasion of the cornea be observed, then the treatment is precisely the same as if the neurosurgeon has produced it through desensitizing the cornea by complete section of the fifth cranial nerve, as in the total removal of a cerebellopontile tumor or ganglion destruction for tic douloureux. Following these two procedures there is often the added complication of facial paralysis with corneal exposure and paralysis of lacrimation. We must be constantly aware of the fact that sensory loss of the cornea is often accompanied by a paralysis of the lacrimal parasympathetic fibers, resulting in a marked diminution of conjunctival moisture and paralysis of reflex or emotional tearing. Now we have all the undesirable conditions present that are conducive to corneal destruction. This can now be avoided only by permanently suturing the denuded inner lid edges together with nonabsorbable surgical (silk) sutures over the length of more than one-half of the outer part of the palpebral fissure. The same meticulous general care as already described with the moist chamber is continued for at least two weeks, or until the ulcer is well healed. The sutures are removed in 10 days, at which time they may

have already fallen out. The cornea can be inspected by having the patient look strongly toward the open end of the fissure. When it appears normal, the fissure can be gradually lengthened, but never until long after healing is complete. If there is a permanent facial paralysis it may be wise to simply open the lids barely enough to uncover the pupil when the patient is looking straight forward. If the parasympathetic nerves to lacrimation have been temporarily paralyzed by hot water injection of the ganglion or swelling of the tissues following operation for tic douloureux, and have not been cut or irreparably damaged, lacrimation will return to normal when the secretory nerve fibers have regenerated. This may require five or six months. This is the reason for not being too hasty about opening the fissure. Conjunctival moisture from the accessory glands of the lids is always present, even after removal of the main lacrimal gland. This moisture must be preserved at all costs by preventing unnecessary exposure of the cornea to light and air. On rare occasions it will be necessary to suture the lids almost completely, leaving only just enough of an opening directly over the pupil for sight, and at the punctum.

I have the impression that a critical study of the current therapy in herpes of the cornea should be made in terms of the physiological factors which I have mentioned, particularly in relation to the disturbance of lacrimation when the parasympathetic secretory fibers and the ophthalmic division of the fifth nerve have been affected. I should also question the value of the time-honored method of intensive local treatments and of cauterizing the herpetic corneal ulcer as opposed to the treatment I have outlined. Herpes is a self-limited disorder, which heals spontaneously after a given time if the cornea is kept moist and free of irritants and secondary infection.

Motor Disorders of the Eye Muscles

Gross lesions causing paralysis of the extraocular muscles are usually located in the region of the third, fourth, and sixth cranial nerves in the cranial cavity and only very rarely in the orbit. Paralysis of the third nerve is the commonest, requires surgical correction, and is most commonly from aneurysm of the carotid just inside the skull. Direct pressure is always present, but, strange to say, the nerve is seldom attenuated by compression. Occasionally a benign tumor (epidermoid, chronic abscess, or meningioma) will compress the nerve. Surgical maneuvers near the nerve may temporarily paralyze it even though there has been no actual trauma. Not only is sight terribly crippled because of double vision from third nerve palsy but the lid droops so low that the patient can not see. The latter is often a blessing in disguise, because vision is not disturbed when it is obstructed by the ptosed lid.

The fourth and sixth nerves are not often affected, since they are imbedded fairly deeply and well away from the usual site of tumor growths. They are more commonly affected by intracavernous aneurysm and tumors than from those growing from inside the dura. The sixth nerve is more commonly paralyzed by tumors from general intracranial pressure than from direct impingement. Paralysis of the fourth nerve is not too disabling, and only slight double vision may be noted on extreme downward gaze. A complete paralysis of the third or sixth nerves is incompatible with binocular vision. Fortunately, all of the extraocular nerves have a strong tendency to regenerate, with restoration of complete function to the muscles, when the causative lesion has been removed.

Myoclonia of the facial muscles (facial muscle tic) can be both grotesque in its appearance and a constant discomfort with its queer pulling sensation from the "drag" of all the facial structures from one side of the face, scalp, and neck to the other. A minor manifestation of this phenomenon is the commonly seen—and fortunately temporary—blepharospasm involving only the orbicularis oculi. There is no known cause

for this disorder of involuntary excessive movement when once well established. It comes on suddenly, usually advances, and to my knowledge never diminishes or stops. Occasionally it is severe enough to warrant surgical relief.

If the patient is mentally stable enough to accept facial paralysis as the cost of stopping the tic, the facial nerve should be sectioned. By anastomosing the central end of the spinal accessory nerve to the peripheral end of the sectioned facial nerve some retention of tone and muscle bulk can be preserved. With proper training in syncronizing face and shoulder movements the cosmetic appearance may not be nearly so disfiguring as the uncontrollable facial tic. Most persons are grateful for relief, but occasionally they are still unhappy after the operation. Then it is possible to reestablish function of the facial nerve by suturing the cut ends together in their original position, but the patient must be warned that a return of the tic is certain, although it may be much improved.

Autonomic Nervous System Disorders

Dryness of the cornea and conjunctiva from paralysis of lacrimation is often a very distressing condition, which may jeopardize visual acuity and even blind the eye. If the visual loss is from corneal opacity, which requires corneal resection, transplant, or a relocated pupil, the operation is probably doomed to failure if there is paralysis of the autonomic nerve to the main lacrimal gland, even though passive secretion is present from the lacrimal and lid glands. It would then seem necessary to fully evaluate the state of lacrimation and the nerves which may be involved in controlling its secretion in each patient showing corneal irritation. So as not to confuse the practical discussion of this problem, I shall not attempt to fully describe the intricate, poorly understood physiological central nerve control of lacrimal secretion. It is enough to consider only the effect of disturbances of the peripheral ends of the ophthalmic and maxillary divisions of the fifth (trigeminal) nerve and the parasympathetic efferent pathway for the production of tears through the greater superficial petrosal nerve.

An important afferent pathway for reflex tearing starts in the sensory endings of the cornea, conjunctiva, and other parts of the orbit. Painful or irritable stimuli from these parts increase lacrimation for the obvious protective device of moistening and washing the cornea to protect it from the noxious effects of mechanical irritation from infection or foreign bodies and from drying through excessive air and light exposure. The maxillary division, with its end-organs in the nose, roof of the mouth, and nasopharynx also carries efferent impulses to activate lacrimation. The efferent part of the reflex arc is concerned largely with the parasympathetic fibers in the greater superficial petrosal nerve as it lies beneath the Gasserian ganglion. Trauma or neoplasm of the medial edge of the ganglion or similar lesion involving the greater superficial petrosal nerve result in paralysis of physiologic reflex lacrimation. Diminished lacrimation is noticeable and may be disastrous on section of the greater superficial petrosal nerve beneath the Gasserian ganglion. Experience has been gained concerning this problem from the commonly performed tic douloureux operation at the ganglion through the temporal fossa and injection of the ganglion with hot water. Both of these procedures often destroy portions of the ganglion supplying the three trigeminal branches and the greater superficial petrosal nerve. It appears that simple destruction of the ophthalmic and maxillary divisions of the ganglion paralyzes the reflex secretion of tears from stimulation on the affected side, but not the secretion resulting from emotional stimulation. However, even though ipsilateral afferent reflex paralysis of lacrimation is present the eye is usually sufficiently moist to prevent eye irritation or any serious complication through the crossed mechanism of contralateral efferent impulses. With

ganglion injection, the paralyzed secretory nerve regenerates in a matter of weeks, and so lacrimation returns to normal even though the eye is insensitive. This is usually not true of operative destruction of the greater superficial petrosal nerve, which often occurs with the subtemporal operation. For this reason I and several other surgeons have preferentially performed the operation of Dandy,[3] which sections the sensory root well back of the ganglion by approaching it beneath the cerebellum, thereby avoiding any possible injury to the greater superficial petrosal nerve.

A contracted pupil with ptosis of the upper lid (Horner's syndrome) is a phenomenon of common occurrence and often of utmost significance. It occurs in lesions of the cervical spinal cord at any point, of the eighth cervical or first thoracic nerves, the stellate ganglion, cervical sympathetic chain in the neck, and carotid artery plexus —particularly near the base of the skull. Thus a complete transverse lesion of the cervical cord causes a bilateral Horner syndrome. Tumor pressing on the stellate ganglion causes a unilateral Horner syndrome, as does an aneurysm or thrombotic infiltration of the internal carotid. This does not produce a visual handicap and not even an annoyance. In fact, most persons are unaware of its presence if bilateral removal of the stellate ganglion has been done.

A partial or complete Horner syndrome often indicates an aneurysm or preaneurysmal pathology of the carotid in the cranial canal. Destructive inflammatory lesions in this location may disrupt partially or completely the cervical sympathetic innervation of the dilator muscles of the iris and lid, since these nerves fit closely against the vessel wall in its course from the stellate ganglion to the orbit. Recognition and proper evaluation of this finding will often lead to the diagnosis of carotid arteriosclerosis and the correct interpretation of the cause for visual defects in acuity and fields from concomitant occlusion of carotid branches. In fact, this finding is very important in understanding certain adverse eye phenomena associated with carotid thrombosis and has recently been described.[4]

Migraine must be considered as a problem closely associated with the eye when the pain becomes centered about it. The patient is apt to overemphasize this association and invariably seeks the opinion of the ophthalmologist. Many also consult the neurosurgeon to make sure there is no brain tumor. It is important that both specialists carefully and thoughtfully consider the symptoms and make a thorough examination so that assurance can be given these anxious persons that no organic disease is present. One will occasionally find a serious eye condition or brain tumor when, on cursory study, the case may appear to be typical migraine. Sphenopalatine neuralgia, histaminic cephalgia of the face, buccal neuralgia, nasal neuralgia, and many other illy defined atypical face pains, in my opinion, are all variants of migraine and respond to the same therapy.

All of the migraines occur in the tense, anxious, ambitious, "go getter" type of person with more than usual intelligence and responsibility. It is a part of the personality make-up, as are many other hereditary tendencies. Physiologically migraine appears to be due to vasodilitation of the arteries in the face, neck, shoulder, and base of the skull—excluding the actual brain vessels. It is caused by vasomotor influences as surely as is blushing on embarrassment, palpitating tachycardia on fright, or fainting. Migraine can be controlled by mental and physical rest. Drug therapy with acetylsalicylic acid, caffeine, and codeine gives immediate comfort if given at the very start of an attack and lessens its tendency to recur. Remissions are frequent and may be prolonged. Spontaneous subsidence can be anticipated with aging. Surgery is never curative, but pneumoencephalography or ventriculography may be dramatic in abruptly stopping a distressing episode.

Intracranial Surgical Lesions Affecting Visual Acuity

Intracranial surgical lesions affecting visual acuity are gross space-occupying lesions

inside the cranial cavity closely surrounding the optic nerves and chiasm or, less often, encroaching on the visual tracts or the occipital visual centers.

Tumors growing near the optic nerve and chiasm produce extremely insidious irreversable destructive effects on these structures. So undramatic are their symptoms that comdefects in the other eye are usually present before the neurosurgeon is asked to see the plete unilateral blindness with gross visual patient. When it is realized that practically all of these lesions are benign and can be safely and successfully removed when the first symptoms arise for which the patients seek medical advice, the seriousness of incompetent medical management becomes apparent. We must learn to give the same consideration to tumor growths as the cause for blindness when papilledema, optic atrophy, diminished visual acuity, and field defects are present as we do to its possible etiology in cases of glaucoma, optic neuritis, retinal arteriosclerosis, nephritic retinitis, syphilitic optic neuritis, and sinusitis. I had the heart-breaking experience of a life-long acquaintance coming to me with blindness in one eye of three years' duration, able to count fingers only in the other, and very ill. He had with him a reprint from a reputable nationally distributed medical magazine which gave a detailed account of his case history and cure by sinus operations two years before. Complete removal of a benign meningioma at this late stage, needless to say, did not cure him.

The diagnostic features of surgical disorders of the cranial cavity, among which eye disorders play such an important part, are now taught to medical students and need not be reiterated to a group of modern ophthalmologists. Slowly diminishing visual acuity, increasing cuts in the visual fields, optic atrophy, and choked discs, each by itself, are the only objective signs necessary for a presumptive diagnosis. While every patient with these symptoms must have immediate plain x-rays of the skull, one must not be lulled into complacency by a normal finding, since many surgical lesions cause no roentgenographic defect in the sella, optic foramina, or other skull parts. By intracranial air injection and arteriographic studies the true nature of the eye disorder can usually be accurately ascertained without great risk. Aneurysm, hypophyseal adenomas, Rathke tumors, meningioma, and osteoma are the common lesions, and all are curable by modern surgical methods. Roentgen ray therapy is still in the experimental stage and at best is only palliative. As a curative agent it is useless and often harmful.

Vascular occlusive disease which causes defects in vision is of great importance, not only from the aspect of precision diagnosis but, as knowledge is gained, for appropriate therapy. Its onset may be insidious or sudden, the effect permanent or transient, depending on the point of occlusion in the vascular tree to the entire head. Our attention has been directed to the occasional reversability of sudden retinal blindness and field defects from a more thorough study and understanding of carotid thrombosis in the neck affecting the intracranial distal arteries of the brain. In the past we have been impressed with the sudden permanent visual loss from complete occlusion of a retinal artery or of the posterior cerebral artery which supplies nourishment to the occipital visual centers. We now know that these vessels may not be completely occluded at all but, because of narrowed lumina, they may provide insufficient blood to properly nourish the sensitive visual nerve cells when their source of blood supply has been reduced by a more proximally located thrombosed vessel, probably associated with a temporary drop in blood pressure. This condition obtains with thrombotic occlusion of the common or internal carotid or basilar arteries. This is more dramatically demonstrated if the basilar or carotid artery, one or both, that is not involved, is inadequate to furnish collateral channels for the needs of the brain through the circle of Willis. Visual difficulties are usually associated with other neurological symptoms which point to basilar artery or carotid thrombosis. These are

transient hemiparetic signs and tingling of parts of one side of the body. Headache on the side of the lesion is common. Transient bizzare visual disturbances occur which may be difficult to explain. These attacks may last from a few minutes to a few days and gradually disappear with no residuals as the active thrombotic plaque heals or adequate collateral circulation develops. Recurrences are common, with aggravation of symptoms, but do not necessarily occur. The lesion can be definitely demonstrated by arteriography, and the symptoms can often be reproduced at will by compression of the normal carotid artery. This disorder occurs most commonly in old age but is frequently observed in the very young. Therapy consists of adequate rest, with physical and mental relaxation enforced with mild sedation. Wide-spectrum antibiotics should be given for three weeks. Since the lesion is focal, at times incompletely occlusive, and associated with an inflammatory hemorrhagic clot, it may be considered good therapy to use anticoagulants. But, as in coronary thrombosis, with which this lesion is analogous, there is no unanimity of opinion as to whether anticoagulants prematurely soften the clot and create emboli or encourage further bleeding into the thrombus.

Tumors of the Eyeball, Orbit, and Periorbital Structures

The only lesion involving the globe that commands the attention of the neurosurgeon is the problem of retinoblastoma. The reason for this is the frequent extension of the growth along the optic nerve into the cranial cavity and the low survival rate with intraorbital optic nerve section. If nerve extension has occurred—and no one can say when it has happened—it is obviously necessary to extend the globe and optic nerve removal backward as far as possible, even to the chiasm. This can be accomplished only, and yet very readily, by craniotomy. In October, 1943, I performed, for Shannon, the first bilateral resection of the optic nerves at the chiasm for bilateral retinoblastomas, through only a one-sided craniotomy, in an infant. The unilateral operation had just been recommended and performed by Ray and McLean.[5] Both nerves were tucked into the orbit through enlarged optic foramina so that they could easily be enucleated at a second operation.[6] The necessity for radical removal is based on the fact that somewhere around 25% of these tumors have passed beyond the lamina cribrosa into the optic nerve and more than 30% have extended beyond that point at which the optic nerve had been sectioned.[7] The recent popularity of radiation therapy has discouraged the intracranial surgical approach, which in the past has been thought to be too radical. If x-ray therapy proves to be no better in its final results than in other neurogenic tumors, a more universal return to prechiasm intracranial section to increase the percentage of permanent cures should be critically considered. With the improved neurosurgical techniques the craniotomy section should carry a very low operative mortality. A reevaluation by comparison of the results in similar groups of cases treated by radiation therapy, prechiasmal section, and enucleation over a 5- or 10-year period seems to be badly needed, since it has been shown that intracranial extension has been the cause of death in a high percentage of instances (47%) according to Merriam.[8]

We can hardly ignore the obvious fact that the mortality from retinoblastoma has been lowered in recent years by the surgeons' insistance on section of the optic nerve farther and farther toward the optic foramen when enucleation has been resorted to. For this same reason, intracranial resection of the optic nerve should still further lower the mortality.

Benign growths in the orbit are often found as primary lesions, while malignant tumor may involve it from direct extension or distant metastasis. Malignancy in the orbit is incurable, and palliation of some type is the only therapy warranted. Trigeminal ganglion injection with boiling water should be done for pain. Osteomas, lipomas, chondromas, dermoid cysts, neurofibromas, mu-

coceles of the sinuses, and other rare benign lesions are amenable to intracranial removal by craniotomy when surgical maneuvers may be impossible through the palpebral fissure. By removing the roof and lateral wall of the orbit it is possible to get wide exposure of the optic nerve, globe, and all the surrounding structures without disrupting the function of the nerves or extraocular muscles. The risk from such a procedure is very low, and the cosmetic result is excellent.

Malignant Exophthalmos

Slowly progressive unilateral or bilateral exophthalmos is commonly attributed to thyroid disease. However, it occurs without thyrotoxicosis and in the absence of a past thyroidectomy. There is good reason to believe that thyroid surgery may actually increase the proptosis by interfering with the venous and lymphatic drainage from the orbits. When the eyeballs protrude so far that the lids can no longer cover the cornea, drying occurs, with ulceration and infection. Loss of vision, and probably the eye, is inevitable if the cornea is not promptly covered by the eyelids. This simple admonition is too infrequently remembered. Its value is readily understood if we keep in mind the not too widely known fact that recovery occurs spontaneously in malignant exophthalmos if intraorbital infection is prevented. This may take as long as nine months or even one year if the eye is properly treated, but regress it certainly will, as the lymphatic channels become reestablished through the face tissues, neck, and into the chest. The lids must be permanently closed over the cornea by simple suture of the denuded lid margins up to the punctum. After 10 days union will be firm and nothing can separate the lids if the procedure is performed properly. It is amazing how easily a massive proptosed eye can be completely covered if the suturing is done across almost the entire palpebral fissure. If by chance it is found impossible to close the lids without too great a tension, a relaxing incision should be made above the eyebrow to lower the lid. This should be made ½ in. (1.25 cm.) above the eyebrow and parallel to it. Its length is determined by the need for relaxing the upper lid. Skin should be grafted to fill the defect above to promote prompt healing. This can be removed when healing of the cornea and the proptosis has receded. A moist chamber is applied and antibiotics are given until the eye is out of danger. When the corneal ulcer has healed, the lids can be gradually opened from the inner corner until the palpebral fissue is open enough to expose the pupil for sight.

With meticulous attention and a well-planned and well-executed lid closure, there is probably no need for the Naffziger orbital decompression operation[9] through craniotomy. Indeed this operation in my experience has aggravated the orbital edema and proptosis, and I doubt very much if I shall ever employ it again.

Summary

A modern approach for treating eye disorders through closely coordinating the information and skills of the ophthalmologist and neurosurgeon is discussed. Of particular and increasing importance are the new discoveries and perfected mechanical appliances and methods available to the surgeon at the present time.

11th and Sansom Sts. (7).

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Case Reports

Unusual Ocular Lesions in a Case of Systemic Lupus Erythematosus

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In the clinic of the Cincinnati General Hospital I had occasion to observe and to follow, for about one year, a patient who was admitted several times to the Department of Dermatology with the diagnosis of systemic lupus erythematosus. Among ocular lesions reported to occur in patients suffering from lupus erythematosus, cotton-wool exudates, scattered retinal hemorrhages, edema of the optic nerve, cytoid bodies, exudative retinal detachments, periphlebitis retinalis, and optic nerve atrophy have been observed; I wish to report about a patient who, suffering from lupus erythematosus, showed a fundus lesion which, to my knowledge, has not before been described.

A 37-year-old Negro woman had suffered from a skin rash, erythematous and maculopapillary lesions and crusted plaques, on her face and upper extremities, with areas of vitiligo, and from chest and abdominal pain and arthralgia since early 1953. Her past history revealed no serious disease; her family and social history were not contributory. Morphology of the cutaneous lesions, evidence of slight renal involvement, leukopenia, positive L. E. cell findings, and skin biopsy were considered as diagnostic proof of systemic lupus erythematosus. In 1955, clinical and laboratory findings confirmed this diagnosis and permitted exclusion of syphilis, tuberculosis, typhoid, paratyphoid, brucellosis, and toxoplasmosis. Her blood pressure readings varied between 130/88 and 125/90 mm. Hg; during the treatment with hydrocortisone (see later) the highest reading was 140/100 mm. Hg. Urine analysis and blood chemistry examination, including B. U. N. and CO_2-combining power, showed all data to be within normal limits. The patient was given chloroquine phosphate, and her condition was well controlled while she was taking 250 mg. twice a day, until March, 1955, when she began to complain that everything seemed very dark to her.

On March 8, 1955, the patient was seen for the first time in the eye clinic. Ocular adnexa, lacrimal apparatus, the external muscles, and both anterior segments were normal except for a few superficial corneal nebulae and for bilateral diffuse atrophy or hypoplasia in the lower half of the irises between the 6 and 7 o'clock positions in the right eye, between the 5 and 6 o'clock positions in the left eye. Media were transparent; both discs were normal; the arteries were narrow and irregular in width, at places so thin that they became almost invisible; the veins were normal. The macular regions were grayish-brown, and the foveolar reflexes were absent. Refraction was as follows: O. D. $+0.25+0.25\times45$; O. S. $+0.25+0.25\times75$. Visual acuity, with and without correction, was right eye 20/20, left eye 20/25. Accommodation seemed to be slightly weaker than the normal corresponding to the patient's age. Chloroquin was discontinued because of the suspicion

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that it might have caused ocular disturbances.

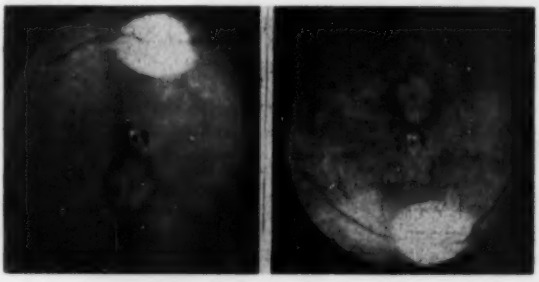
In June, 1955, the patient was readmitted to the hospital because of a recurrence of symptoms of lupus erythematosus and was treated with hydrocortisone, 20 mg. twice a day. Because of an acute abdominal episode with paralytic ileus, interpreted as lupus erythematosus crisis, she was treated intravenously with hydrocortisone. Within two days her abdominal symptoms subsided and oral hydrocortisone treatment was resumed, then gradually withdrawn while increasing amounts of hydroxychloroquine (7-chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino]-quinoline) (Plaquenil) were administered. During the last days of June, a black spot, slightly smaller than the disc, appeared in the macular region of each eye. In the center of the black spot, a small whitish area appeared which was interpreted as early atrophy. No change in the appearance of the vessels was noted. On July 6, the fundi were unchanged; the visual acuity was 20/40 in the right eye and 20/30 in the left eye.

On July 17, the area of atrophy appeared larger and surrounded by a dense border of pigment. In the right eye, in the inferior temporal quadrant, near to the equator, a cotton-wool exudate was visible. In the peripheral inferior fundus of the left eye tiny granules of pigment were visible, located in the superficial layers of the retina. In the same eye, a small pigment spot was present two disc diameters below, and nasally from, the disc. The patient was discharged early in August with prescribed treatment of hydrocortisone 10 mg. and hydroxycholoroquine 500 mg. daily.

On reexamination, in September, the atrophy of the macular region appeared larger, showing a pigmented border as before and small reddish areas in both foveae. The cotton-wool exudate had disappeared. The visual acuity was 20/40 in the right eye and 20/70 in the left eye; the visual fields, both central and peripheral, were constricted to 10 degrees; a central scotoma could not be outlined (see fundus photographs).

During the months of October to December the macular region did not change noticeably; the atrophy became more marked, the pigmented border more pronounced. In October the patient was readmitted to the hospital because of recurrence of her skin lesions and joint pains. At that time she did not respond well to 250 mg. of hydrocortisone administered daily; therefore prednisolone was substituted and continued with some success until Dec. 23, 1955, at which time my ophthalmologic observation was discontinued.

This case is reported because I found no report in the literature of fundus lesions caused by lupus erythematosus similar to those of the patient. I think that her lesions were due to lupus erythematosus because of the simultaneous presence of other fundus lesions commonly related to lupus erythematosus and also because of concurrent appearance of the ocular alterations and recurrences of lupus erythematosus. Labora-



Aspect of the fundi of both eyes in September, 1955.

tory examinations permitted exclusion of infectious etiology of the retinal lesions described; it was more difficult to differentiate these lesions from macular degeneration of the tapetoretinal type. I think that chloroquine can be ruled out as a causative factor, since discontinuation of this drug did not result in improvement.

Dr. K. W. Ascher gave helpful advice.

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Leakage of Spinal Fluid into Upper Lid Following Trauma

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The case reported is one of an orbital fracture with laceration of the dura and leakage of spinal fluid into the subcutaneous tissue of the upper lid. Aside from the fact that a similar case could not be found in the consulted literature, this case seemed to be of interest because (1) the unusual type of cranial fracture was probably facilitated by the anatomical characteristics of the patient (9 months old) and (2) the initial characteristics of this case were those of a common traumatic unilateral lid hematoma.

Report of Case

A 9-month-old baby was urgently admitted on April 20, 1954, to the Neurosurgical Service of the Boston City Hospital following an automobile accident which had occurred some 20 minutes previously. Remote and familial history were negative. The examination of the patient showed blood pressure, 100/60; pulse rate, 120; respiration rate, 40. The chest and abdomen were negative. The anterior fontanelle was nearly occluded, and no excess pressure was evident. Although the patient was comatose, he responded to stimulation by crying. There was some rigidity of the neck, and the left arm responded feebly to stimuli. Reflexes were equivocal throughout but diminished on the left. Plantar reflexes were present and equal.

The ocular examination showed contusion and hematoma of the upper lid of the left eye; there was a slight subconjunctival hemorrhage. The left pupil was larger than the right and did not react to light. The optic media and the fundus of the eye were normal. The right eye was normal.

X-ray examination on admission revealed a probable fracture of the right parietal skull.

Laboratory Examinations. — The usual admission laboratory determinations were performed, including urine analyses, which were normal, and three hematocrit determinations, that were reported as 30% on April 20 and 33% on the morning and afternoon of April 21. Blood chemistry studies on April 21 showed 102 mg. of chloride per 100 cc. and 56 vol. % of CO_2. Routine throat cultures were performed on April 24. A total of eight diagnostic and therapeutic lumbar punctures were done. On the day of admission, the lumbar puncture, with which 8 cc. of spinal fluid was obtained, showed an initial pressure of 130 mm. and a final pressure of 100 mm. Fluid was grossly bloody, with a total protein of 480 mg/100 cc. of cerebral spinal fluid. The last lumbar puncture, performed on May 18, revealed a pressure of 120/100. The fluid was colorless and contained 90 red blood cells and 3 white blood cells; the total protein was 17 mg/100 cc.; the sugar, 82 mg/100 cc.

Course.—The child was placed on a regimen of careful neurologic observation. From the eye standpoint there was little or no variation of the lid hematoma in the days that followed. The left pupil still remained fixed and dilated.

On April 24 respiratory wheezing was noted in both lung fields and pediatric consultation led to a diagnosis of pneumonitis, for which the patient was treated with peni-

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cillin. For several days the temperature varied from 100 to 102 F. On April 26 x-ray films of the skull did not show definite lines of fracture. Since the condition of the lid hematoma was almost unchanged, it was thought that a hematic cyst had developed in the lid subcutaneously. On May 21 an incision of the lid hematoma was proposed, but Dr. Regan opposed this plan, suspecting intracranial communication.

In the following days, the red color of the hematoma began to clear up rapidly, without passing through the variations of color characteristic of resorbing blood pigment. The lid swelling acquired the aspect of a progressively growing lid edema. This edema increased to such an extent that the superior lid margin appeared displaced below the inferior lid by more than 1 cm., and it became difficult to separate the lids even when using everters.

On May 2 multiple stereo skull films were taken and showed an irregularity of the orbital rim between 12 and 3 o'clock consistent with a fracture. In view of this, it was felt by Dr. Regan that aspiration of the palpebral fluid should be performed, followed by a craniotomy. This was done on May 5, 1954. Aspiration showed fluid clear and slightly yellow, with a total protein of 678 mg/100 cc. and a sugar content of 28 mg/100 cc. Just prior to this aspiration, a lumbar puncture was performed for the purpose of instilling 1 cc. phenolsulfonphthalein, and the total protein and sugar were 22 mg/100 cc. and 43 mg/100 cc., respectively. No dye was seen in the orbital fluid on NaOH titration. The cranial exploration revealed the superior orbital plate fractured, with a downward displacement and laceration of dura, arachnoid, and cortical mantle of the orbital surface of the frontal lobe. Cerebrospinal fluid was seen to come forth from the meningeal tear. These defects were suitably repaired. Incisions in the upper palpebral conjunctiva were performed in order to facilitate the drainage of fluid soaking the tissues. The postoperative course was uncomplicated from the neurosurgical standpoint, and the lid edema disappeared within a few days. There remained, however, ptosis and paresis of the left superior rectus. The pupil reacted normally to light.

Summary and Comment

A 9-month-old baby showed slight signs of intracranial hypertension and a lid hematoma of the left eye following trauma. The eye appeared to be normal except for a slight ecchymosis of the bulbar conjunctiva and a dilated and rigid pupil, which was considered to be secondary to the direct trauma on the eye. The right eye appeared to be normal.

It is often difficult to differentiate between a "black eye" and a hematoma secondary to fracture of the orbit. The characteristics first observed in our patient resembled those of a hematoma of the superior lid. In fact, according to Walsh,[1] in orbital fractures the blood appears after several hours or days. Furthermore, in these cases the inferior lid contains more blood than the superior one and there is frequently a butterfly distribution of the hemorrhage due to the fact that the blood terminates at the level of the orbital fascia.

About 10 days after the trauma, the hematoma began to disappear without passing through the various characteristic phases of resorption. The superior lid acquired a strongly edematous aspect, greatly increasing in volume. The fact that there was first only a small amount of chemosis of the bulbar conjunctiva made us think that the edema was prevalently outside the orbital fascia. A prolapse of the superior fornix occurred, however, toward the final stages before surgery. The initial x-rays did not definitely show signs of cranial fractures. Repeated x-rays on the 12th day showed on the supraorbital margin and on the roof of the orbit a line of fracture located in an unusual region and with a tortuous aspect which is uncommon, at least for adults.

Craniotomy showed a fracture with rupture of the meninges in the left supraorbital

area, leaking of spinal fluid into the subcutaneous tissue of the upper lid, and signs of contusion of the left frontal lobe. After surgery and resorption of the lid edema, partial paresis of the third nerve (levator and superior rectus) remained, while the left pupil reacquired a normal size and a normal light reflex.

The preparation of this case report was aided considerably by contributions from the Neurosurgical Service, Boston City Hospital.

Clinica Oculistica Policlinica.

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Annual Reviews

The Uveal Tract

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I. Introduction

The world literature pertaining to the uvea is voluminous and often repetitious. Recently, however, there has been substantial advancement in our knowledge of the etiology of uveal inflammations. A simple reiteration of the published articles would contribute little to our knowledge. Therefore, I shall attempt to emphasize the advancements and comment on the more prominent articles published within the past year.

Allen C. Woods' book on endogenous uveitis, published during 1956, is without doubt the greatest single work on this subject.[1] The book is the result of a life-long study of the uvea. The contents are rich with valuable interpretations of the newer concepts of endogenous uveitis. A brief review can give only the high spots of this complicated subject, but, in the limited space available, I have summarized some of the more important sections and injected scattered comments where possible.

Woods' classification of endogenous uveitis is complete and serves as a splendid outline for study.

Nomenclature

A. Granulomatous uveitis

B. Nongranulomatous uveitis

Pathogenesis

A. Granulomatous uveitis is caused by actual invasion into the uvea of a causative agent in living form. It may be caused by the following agents:

1. Nonpyogenic organisms
   (*a*) Syphilis
   (*b*) Tuberculosis
   (*c*) Brucellosis
   (*d*) Leptospirosis
   (*e*) Others (leprosy, etc.)
2. Filterable virus and Rickettsia
   (*a*) Behcet's syndrome
   (*b*) Vogt-Koyanagi-Harada syndrome
   (*c*) Herpes simplex
   (*d*) Herpes zoster
   (*e*) Lymphogranuloma venereum
   (*f*) Undetermined and unknown virus
3. Protozoan infections
   (*a*) Trypanosomiasis
   (*b*) Toxoplasmosis
4. Fungus infections
   (*a*) Actinomycosis
   (*b*) Blastomycosis
   (*c*) Histoplasmosis
   (*d*) Others
5. Helminth infections
   (*a*) Nematodes
      (1) Onchocerciasis
      (2) Ancylostoma larvae
   (*b*) Cestodes
      (1) Taenia echinococcus
      (2) Cysticercus cellulosae
   (*c*) Diptera larvae
6. Unknown agents
   (*a*) Sympathetic ophthalmia
   (*b*) Sarcoidosis

Nearly all of the above agents have been recovered from eyes suffering with granulomatous uveitis. Every case cannot be proved, because of technical reasons, but a sufficient number of isolated cases with proved etiology substantiate Woods' theory.

The known sensitivity to uveal pigment in sympathetic ophthalmia is only part of the story. An additional factor may be viral or infectious. The same situation is true in sarcoidosis, where lesions histologically resemble tuberculosis. However, much evidence suggests another etiology. The fact that an agent has not been found fails to prove that a causative agent is not present in the ocular tissues.

As laboratory tests have been developed, there has been a significant shift in the

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etiologic diagnosis of granulomatous uveitis. The first series, published in 1941 * (as compared with two successive series, in 1944 and 1953) showed the following findings:

Etiology	Per Cent of Cases		
	1941	1944	1953
Tuberculosis	79	52	23
Syphilis	16	17	7
Sarcoidosis	1	10	6
Brucellosis	1	10	7
Toxoplasmosis	0	0	26
Miscellaneous (viral)	3	5	13
Unknown	0†	6	18

† In this series all cases were assigned.

Explaining the great significance of this Tabulation illuminates the progress of our knowledge of the disease. The marked reduction of syphilis is due to the general decrease in the frequency of the disease in the last 10 years. The recognition of the relative frequency of Brucella infections in 1944 subtracted some cases from the category of tuberculosis. Later, in 1953, the appreciation of the role played by toxoplasmosis further lowered the percentage of cases diagnosed as tuberculosis. The increase in the number classed under unknown is due to the fact that stricter criteria were employed for the last two series. As the years progress, no doubt many other cases can be definitely classified under a known heading. The more accurate the diagnosis the greater the hope for specific treatment.

The absorption of toxins from a focus of infection in a state of hypersensitivity creates a toxic insult and may produce nongranulomatous uveitis. A similar toxic insult may result from a nonbacterial allergic reaction. In sensitized animals the injection of horse serum causes nongranulomatous uveitis. Some observers have recovered organisms from the aqueous in nongranulomatous uveitis; however, desensitization or removal of a focus of infection often results in a cure. Some 80% of nongranulomatous uveitis cases demonstrate a hypersensitivity to streptococci. Such a finding suggests the important role played by streptococci in this disease.

The pictures of granulomatous and nongranulomatous uveitis may be typical, but some cases present signs and symptoms of both diseases.

The granulomatous lesions are dependent on a specific infecting agent. The onset is slow, and the disease may heal without recurrences. As the disease progresses, epithelial cells form "mutton fat" deposits and the cellular infiltrates form nodules in the iris. As the infection subsides, the eye whitens. The corneal deposits may disappear and the iris nodules either absorb or leave fibroid scars. Residual organic damage is the rule.

When the infection fails to subside, organic changes in the form of posterior synechiae, cyclitic membrane, secondary cataract, and even phthisis bulbi may result. If the disease involves the posterior segment, there is marked clouding of the vitreous. Single or multiple choroidal exudates are characteristic. However, the infection may be diffuse and include the whole fundus in a dense pigmented scar.

Pathologically, there is at first an outpouring of leukocytes, which are quickly replaced by large mononuclear cells that invade the tissues. Collections of epithelial cells give the typical granulomatous appearance. Necrosis of the inflammatory cells results in connective tissue scars.

Much work has been done to combine the Vogt-Koyanagi and Harada syndromes into one disease. Its close association to sympathetic ophthalmia, both clinically and pathologically, is striking.

Uveitis of viral origin is a nonspecific inflammation that shows a predilection for tissues derived from embryonic ectoderm. Herpes zoster also involves the perineurium, with necrosis of the arterial walls.

Among the protozoan infections, toxoplasmosis has gained great importance since Wilder identified the Toxoplasma organisms in enucleated eyes. Many cases can now be correctly distinguished from tuberculosis.

* Reference 1, Table 1, p. 22.

In uveitis of unknown etiology, massive cellular reaction with little inflammatory response is characteristic of sympathetic ophthalmia. However, the systemic disease of sarcoidosis presents a picture of discrete nodules on the iris. Heerfordt's disease is now recognized to be sarcoidosis.

A single allergic insult from bacterial antigen hypersensitivity is a cause for nongranulomatous uveitis. Such an infection is usually self-limited. If the antibody appetite is not satisfied and the tissues are constantly bombarded by the antigen, the attack is prolonged and organic changes take place that may simulate advanced granulomatous uveitis. The epithelial reaction in chronic cases resembles rheumatic nodules.

A certain number of cases have characteristics of both granulomatous and nongranulomatous uveitis. The same organism that produces granulomatous uveitis may produce sufficient hypersensitivity to intensify the reaction and cause the condition to resemble nongranulomatous uveitis.

Chapter 3 of Woods' book is devoted entirely to diagnosis. It is of great importance to differentiate granulomatous from nongranulomatous uveitis. This is the first responsibility. A careful history may enable the ophthalmologist to make a shrewd guess as to the etiology of the uveitis.

An ophthalmic examination should be careful and complete, including every available test that may shed light on the nature of the condition. After a careful history and complete examination the differential diagnosis is often easy. However, certain cases may be confusing and require special tests to establish the exact nature of the case. As soon as the clinical diagnosis has been made, a medical survey should be done. Since the internist is rarely aware of the complexity of the problem, it is necessary for the ophthalmologist to captain the search and evaluate the findings. The uveitis may be clearly of one type and certain tests can be omitted, but this is the ophthalmologist's responsibility.

The diagnostic search in granulomatous uveitis must include the most prevalent granulomatous diseases, but if the history or examination suggests one of the less common diseases the study should be expanded to include all such infections. Therapeutic tests are often valuable.

Toxoplasmosis has proved to be an important cause of granulomatous uveitis. The congenital infection is sufficiently typical to offer little difficulty. Acquired toxoplasmosis may be difficult to establish because the serologic test merely indicates the prevalence of human infection. Ocular involvement is probably a rare manifestation in infected persons; therefore, the tests merely record the incidence of the disease. Infections of the eye are not characteristic and resemble other diseases. The Sabin test has not been standardized.

Sympathetic ophthalmia is not often a diagnostic problem, because there is a history of injury to one eye with inflammatory response in the fellow eye. The pigment test may be helpful, but it is not specific for sympathetic ophthalmia.

Nodular iritis should always suggest sarcoidosis, but the final diagnosis must depend on systemic findings, the most important of which are (1) nodular skin lesions, (2) lymphadenopathy and results of histologic study, (3) radiographic changes in the lungs and phalanges, (4) rise in serum globulin, and (5) anergy to tuberculin.

In nongranulomatous uveitis the clinical diagnosis can usually be made from the history and ocular symptomatology. Isolation of the offending allergen may be a complex problem. Fortunately, streptococci, staphylococci, and gonococci account for more than 80% of nongranulomatous uveitis.

Exclusive of staphylococci, Streptococcus is the most frequent organism in foci of infection. Rheumatoid arthritis, probably an allergic reaction, is thought to be caused by streptococcal hypersensitivity. Intradermal skin tests from the 12 subgroups of

β-hemolytic streptococci account for a large percentage of those cases due to streptococcal infection. If a definite focus of infection is discovered, bacteria should be cultured and tests made from the bacteria isolated. Gonococcal hypersensitivity is a known cause for nongranulomatous uveitis, but since the advent of penicillin the problem has greatly decreased.

Search beyond the common offenders may try the endurance of both the ophthalmologist and patient, with very little reward. If there is some specific sign that points toward a certain organism, then, by all means, tests should be made.

A therapeutic dose of a specific vaccine may cause a marked reaction in the eye—this is dangerous. A systemic reaction without a flare-up in the eye is a strong argument against a relationship to a certain vaccine. Definie improvement following desensitization is evidence for the causative agent.

Treatment is divided into specific and nonspecific therapy. This is true for both granulomatous and nongranulomatous uveitis.

General hygienic measures are designed to improve the general health of the patient by insuring ample rest and sleep, well-balanced diet, proper elimination, and relief from nervous tension. If such a program cannot be carried out at home, dramatic improvement may follow hospitalization.

Local procedures include mydriasis, that puts the ciliary body at rest and breaks synechiae or prevents their formation. It relieves much of the discomfort from photophobia and congestion. The actual therapeutic effect of heat is questionable, but it is soothing to the patient. Paracentesis may temporarily relieve secondary glaucoma until medical means can take over. Irradiation therapy is of questionable value, and the attending dangers may outweigh the advantages.

The corticosteroids may eleviate symptoms and reduce the inflammatory response, but there are also real contraindications for their use. The inhibition of inflammatory response may be dramatic and prevent permanent damage from the fixed cells. Response in the nongranulomatous cases may be very effective, but corticosteroid therapy is contraindicated in all granulomatous infections except sarcoidosis and sympathetic ophthalmia. The introduction of nonspecific protein therapy increases the immune titer. Later there is a response similar to that seen in corticosteroid therapy. Intravenous injection of triple typhoid vaccine is the agent of choice.

Antibiotics and sulfonamides have been tried extensively, but they are of little value except in specific infections in granulomatous diseases. Mechlorethamine (nitrogen mustard) had given promising results but needs more study. Phenylbutazone (Butazolidin) gives an effect similar to that of cortisone, but this not accomplished by affecting the adrenocorticosteroid mechanism. Serious side-effects involving the hemopoietic system or kidneys make the use of the drug relatively dangerous. Further study may prove this to be a valuable addition to our armamentarium. Specific therapy in granulomatous uveitis is either topical, oral, or parenteral administration of a specific drug that has a bacteriostatic or bactericidal effect or the use of immunological procedures to increase the resistance of the patient's infection; sulfonamides and broad-spectrum antibiotics are helpful in the larger virus infections, but unfortunately the smaller viruses are not affected.

Once the diagnosis of toxoplasmosis has been established, there are several chemotherapeutic agents that are effective experimentally; however, human response is not quite so definite.

Specific treatment for nongranulomatous uveitis is designed to reduce the hypersensitive state of the patient. This is accomplished by keeping the patient from contact with the allergen or by removing the specific tissue sensitivity.

Corticosteroids may block the sensitivity reaction if the specific substance cannot be eliminated or found. If the specific allergen is determined, a course in desensitization is beneficial in a high percentage of cases.

Anatomy and Physiology

The research done on the choroid by Wudka and Leopold [2,3] is a model both in presentation and in thoroughness. The intriguing technique used to study the effects of various drugs on the choroid showed that agents which which act directly on the vessels produce vasoconstriction. Agents given systemically cause changes in the vessels only when systemic effects are noted.

Wybar [4] injected the retinal and uveal veins about the optic nerve and found that a small percentage of cases showed definite anastomosis. The presence of such anastomosis could explain the failure of glaucoma to devolop following occlusion of the central retinal vein. Arterial anastomosis was more difficult to demonstrate.

Apter [5] concluded in her investigation that the parasympathetic nerves change the size of the pupil by stimulation or inhibition of the constrictor muscle. The dilator acts passively. Sympathomimetic drugs affect the pupil by changing the caliber of the iris blood vessels.

The presence of peripheral iris crypts produces an irregular anterior surface on the iris. The presence of these crypts can prevent blockage of filtration. Miotics may stretch the iris and destroy the effect of the crypts and cause occlusion of the angle in the narrow angle type of glaucoma.[6]

Kurus [7] identified small unipolar and bipolar ganglion cells in the anterior choroid. The cells are controlled by the ciliary ganglion and may have a regulatory function. There are three types of pericytes found around the small choroidal vessels. Both longitudinal and circular pericytes surround the larger vessels, but the pericytes become irregularly arranged around the capillaries. These cells may be akin to smooth muscle and influence the contraction of the vessels. [8]

Cowan,[9] in his de Schweinitz lecture, discussed ocular pigment and defined the melanoblast, the embryonic cell that may or may not contain pigment; the melanocyte, which is the mature cell, and the melanophage, which is a histiocyte that has phagocytized pigment. Blood staining of the cornea may occur without an elevated tension, and the blood pigment is located on the posterior surface of the cornea. Holmberg [10] studied the nonpigmented epithelium with the electron microscope and found a complicated intracellular canal system. Such findings suggest a secretory function of these cells. Further study by the injection of dyes or radioactive tracer substance may be of value in completing this experiment.

Certain characteristic structures are found within the ciliary epithelial cells by which the sex of the subject may be determined, but clinical application of this finding has not been made.[11]

Congenital Defects

Callahan [12] reported a case of a young girl with multiple malformations of the iris; namely, atrophy, holes, eccentric pupil, and vascular tissue on the anterior surface. Histological study of one eye was made after repeated antiglaucoma operations. The changes described were indistinguishable from those found in glaucoma of long standing. A typical coloboma of the optic nerve and disc may be associated with cavernous angioma of the face.[13]

Degenerative Diseases

Essential and progressive iris atrophy is believed to be a condition similar to Fuchs' heterochromia.[14] Chandler [15] studied six cases which had iris atrophy, corneal dystrophy with edema, and glaucoma. Early operation to maintain the tension below 20 mg. Hg. resulted in clearing of the cornea.

Obliteration of a long posterior and anterior ciliary artery during operation resulted in hyphema, with necrosis of the iris due to an anemic infarct.[16]

Among the papers discussing tapetoretinal degeneration and choroidal sclerosis, Sorsby[17] described two families in which male members of each family had marked choroidal sclerosis and choroidal atrophy. The female members presented central fundus changes. If the atrophic changes found in one one family represent choroideremia, then the choroidal sclerosis must be accepted as an intermediate stage of the disease. François[18] reported typical fundus changes of tapetoretinal degeneration in elderly patients without pigmentation. Hoza[19] finds it difficult to classify choroideremia as a separate entity from Fuchs' gyrate atrophy and retinal pigmentary degeneration. Marked choroidal atrophy may be due to involvement of the short posterior ciliary arteries.[20]

Angioid streaks may be present long before the skin lesions appear to complete the picture of pseudoxanthoma elasticum (Groenblad-Standberg's syndrome).[21] Eventually the skin lesions will develop.[22,23] Macular degeneration is often present in pseudoxanthoma elasticum and may be a fundamental part of the disease.[24]

The varied picture in macular degeneration may be caused by its effect on the different components of the lamina vitrea. In the edematous phase the collagen tissue is affected, while the atrophic phase involves the elastic element.[25] Mylius[26] believes that the presence of lipoid substances in the arteriosclerotic vessels about the macula produces senile macular degeneration. Administration of heparin resulted in definite improvement of his cases. Fuchs[27] attempted to classify various types of drusen of the lamina vitrea and suggested a geographical significance to the various types of drusen. Pathological specimens were not presented. Therefore, the exact nature of the various lesions is not clear.

A careful study of patients exposed to solar eclipse demonstrated varying degrees of burn. The burns of the retina were compared to burns of the skin and varied from simple hyperemia to destruction of the macula from necrosis and coagulation. The injury is based on the focusing of infrared rays on the macula. Therefore, uncorrected myopes were the least susceptible.[28] Rose et al. and Landesberg[29,30] described chorioretinal burns following exposure from atomic explosions. The lesions were similar to eclipse blindness. The severity of the burns depended on (1) size of the explosion, (2) distance from explosion, (3) duration of exposure as limited by blink reflex, (4) transparency of media, and (5) size of pupil. Exposure to heavy doses of x-rays to the head and eyes causes an iridocyclitis to develop after irradiation. The iris changes resemble essential iris atrophy seen in humans.[32]

Snell[33] found no attempt at fibroblastic repair of an injured iris in experimental animals. It is suggested that the aqueous may be the inhibitory factor that prevents fibroblastic repair.

Localized atrophy has been found in the choroid in areas of retinal atrophy and holes. Such choroidal changes may explain the cause of retinal holes with subsequent detachment of the retina.[34]

Inflammations

Extensive research has continued in the quest for definite etiologic agents causing uveitis. In rabbits with tuberculous infection of the eye there is a higher antibody titer in the aqueous than in the blood. However, where both systemic and ocular infection is present the titer in the serum is equal to that in the aqueous.[35,36] Among humans with granulomatous uveitis, a small group had a high hemagglutination titer of the aqueous suggesting a tuberculous origin but the larger portion of the cases were not due to tuberculosis. Agarwall's[37] study of the aqueous in uveitis showed the presence of polymorphonuclear leukocytes, with in-

creased protein, in bacterial uveitis. The granulomatous uveitis showed a preponderance of lymphocytes and mononuclear cells, along with elevated protein. The offending organism was isolated in some cases. Verrey,[38] in his study of the aqueous, further emphasized the importance of this test. Goldmann [39,40] has studied the reactions of specific antibodies taken from the aqueous in cases of uveitis. Conclusive findings have not yet been established. A clinical and statistical survey of uveitis divided the disease into four groups: A. collagen disease, 20%; B. local virus infections, 38%; C. systemic disease, 15%; D. unclassified, 37%. None of the series was ascribed to tuberculosis, and, among the therapeutic agents used, cortisone was found beneficial in Group A, of doubtful value in Group B, and dangerous in Group C. With further study this new concept may add to our knowledge of uveitis. Woods [41] found a more acute reaction in sensitized rabbits following the injection of horse serum than with bacterial antigen. The injection of albumen into the anterior chamber caused an acute iridocyclitis, but the posterior uvea was not affected even after intravitreous injection.[42] Schirmer [43] found that iridocyclitis caused by horse serum was improved by the administration of acetazoleamide (Diamox).

With the increased interest in and knowledge of toxoplasmosis, a study section headed by Hogan [44] met to establish criteria for diagnosis and treatment of the disease. Pyrimethamine (Daraprim) is an effective medication if given in near toxic doses, but such a procedure is not without danger to the patient.[45] In a given case, the toxoplasmic antibodies must first increase and then decrease in order to establish a positive reaction for the disease.[46-48] The dye test may be positive while accompanied by a negative complement fixation test. If the compliment fixation test later becomes positive, such a reaction is a good indication of recent infection. However, if the test remains negative, the positive dye test indicates a chronic infection.[49] Bruna [50] inoculated egg yolk sac with Toxoplasma organisms and noted definite histologic changes. The parasite had a specific affinity for vascular tissue. The most seriously affected tissue was the uvea, but no signs were seen in the avascular retina.

A number of individual cases of toxoplasmosis have been reported, one of which was the first recorded case from South Africa.[51-53]

Behcet's disease produces iridocyclitis, with hypopyon, apthous ulcers, and ulceration of the genitalia. Sezer [53] isolated a virus that was neutralized by antibodies taken from the blood of convalescent patients. On rare occasions the uveitis is unilateral.[55] One case of Behcet's disease has been reported in this country.[56]

In a series of 150 cases of primary tuberculosis in adolescents, 12% had fundus lesions.[57] Hanno and Spaeth compared tuberculin reactions in a large series of uveitis patients with those in a similar control group. The positive skin test was not significally different in either group. Their investigation led them to conclude that tuberculosis was not an important etiological factor. On the contrary, since a high percentage of positive reactions was found in both groups, it may be correct to conclude that tuberculosis is a very important factor. In the diffuse uveitis due to tuberculosis no bacilli are found, and the reaction is on an allergic basis.[59] The organisms in a focal lesion due to hematogeneous dissemination of bacteria from a distal focus have been acted upon by the antibodies of the blood and have lost their virulence and power of multiplication. Treatment in a fresh case should avoid reduction of general immunity. Specific therapy should be withheld for at least eight weeks to give natural antibodies a chance to reduce the infection.[60] Isoniazid has been reported to produce a cure in all of eight reported cases,[61] and large doses of ascorbic acid led to attenuation of the tubercular process in experimental animals.[62]

Sympathetic ophthalmia does not occur with uncomplicated trauma to the eye. How-

ever, if the trauma is accompanied by infection sympathetic infection may develop. During the protracted healing, the uvea becomes antigenic.[63,64] Isolation of the viral agents that cause sympathetic opthalmia has not been successful, but material from an involved eye can be injected into the vitreous of a rabbit with resultant acute uveitis. Histologic study reveals a condition resembling sysmpathetic ophthalmia found in humans.

In a monograph Piñeroy Carrión discusses the uveomeningeal syndrome and concludes that the Vogt-Koyanagi and Harada diseases are different manifestations of the same disease. The close relation to sympathetic ophthalmia is also discussed. The author divides the disease into three phases: (*a*) meningoencephalitic, (*b*) uveitis, and (*c*) associated signs. No definite etiologic factor has been established. Samuelly [66] thinks that a psychic component plays a major role in the onset of the Vogt-Koyanagi-Harada syndrome. Several authors have reported cures with the administration of corticotropin (ACTH).[67,68]

Trenkler [69] is said to have reported the first two cases of Leptospira uveitis in humans. A hemorrhagic exudate develops in the aqueous, and a positive titer of 1:6400 was obtained. Another case was reported where Leptospira organisms were recovered from the aqueous.[70] Witmer,[71] in a case of leptospiral uveitis, found the antibody titer of the aqueous of the affected eye to be higher than the titer of the blood. It was concluded that some antibody formation takes place in the uvea.

Streptococcus infection has gained importance as an etiologic factor in uveitis. Among a series of uveitis patients, a significant group showed high antistreptolysin titer, suggesting that the offending organism was Streptococcus.[72,73]

Allergy plays a very definite role in certain types of uveitis. Hoover [74] and Sedan and Guillot [75] reported six cases of nongranulomatous uveitis following the administration of tetanus antitoxin. Woods et al.[76] produced nongranulomatous uveitis experimentally by injecting foreign protein into sensitized animals. Tuberculoid or granulomatous reaction was not found in the animals of this experiment.[77] Necrotizing uveitis accompanied by a systemic collagen disease is thought to be on an allergic basis.[78] Callaghan [79] reported a dramatic cure of uveitis following desensitization to house dust and orris root. In all articles there seems to be agreement that certain cases of uveitis are due to the hypersensitive reaction to a protein-bound antigen from a distal point, whether it be of bacterial origin or not.[80]

An attempt to investigate the relationship of iritis to ankylosing spondylitis produced rather startling figures. Of 15 cases with established spondylitis, 11 had iritis as a presenting symptom. In all cases the exudate in the anterior chamber was gelatinous. The eye findings were sufficiently typical to warrant x-ray of the sacroiliac joints. Cortisone was of little benefit.[81]

Lyda's [82] experimental work on lens-induced uveitis leads to the conclusion that the host must be sensitized by an adjutant injected into the lens at the time of the discission. The use of Staphylococcus toxin caused a definite reaction even though the skin test to lens antigen was weakly positive. Leigh [83] does not entirely agree with this theory, as can be seen by his classification of lens-induced uveitis.

All reports on ocular sarcoidosis came from the British literature. Between 22% and 40% of cases with sarcoidosis have ocular signs. The eye signs may be the presenting symptom. Usually there is a nodular painless iritis developing into a secondary glaucoma from the scarring of the peripheral nodules. Muscle biopsy or even conjuntival biopsy is necessary to fix the diagnosis.[84-87] The relationship of Hodgkin's disease and uveitis should be questioned.[88] Obscure cases of uveitis may be caused by Brucella organisms. Such conditions are apparently rare.[89]

A case of chorioretinitis caused by blastomycosis was reported. Histologic examination revealed the organisms in the choroidal lesions.[90]

Some of the newer drugs have proved effective in diseases of the uveal tract. Trypsin has resulted in a prompt improvement in cases of ocular hemorrhage and uveitis.[91]

Domato[92] has described a drug called Irgapyrine (4-butyl-1,2-diphenyl-3-5-pyrazolidinedione) which is beneficial in iridocyclitis. Its action is similar to that of cortisone, but the only complication is the theoretic lowering of the leukocyte count.

Gordon[93] found the effects of prednisone and prednisolone to be superior to those of cortisone in uveitis. O'Rourke[94] found prednisone to be five times more effective than equal doses of cortisone. Lepri,[95] however, disagrees that prednisone is more effective than cortisone. After two cases of posterior uveitis were treated with cortisone, a detachment of the retina developed in both cases. The detachment may well have been due to the fact that the normal chorioretinal scar failed to form, thereby permitting a detachment of the retina.[96]

Kalt[97] reported a persistent iritis in 60% of patients following antiglaucoma operations. No mention was made of whether steroids were used or not. Redell[98] described necrosis of the iris following the insertion of an acrylic lens. Such a report further emphasizes the danger of such an operation.

In a series of 3000 cases of uveitis Unger[99] found that the course of the disease or frequency of relapse was not altered by tonsillectomy.

According to MacDonald's[100] investigation, 9% of all blindness is the result of uveal disease. This does not include unilateral blindness. Velicky[101] found that patients with recurrent uveitis suffered relapses on changes of the weather. The day before a cold front arrived was the time a significant number of patients had relapses. He believes that a chronic disease is not a constant inflammation but a series of recurrences due to changes in the weather.

Neoplasms—Cysts and Tumors

Prolonged miotic therapy may result in proliferation of the iris pigment epithelium. Cessation of the miotic causes regression of the tumor.[102] The regression of the tumor is as interesting as its formation, since it demonstrates the necessity to have a continual stimulating substance in order to maintain the neoplasia. Newell[103] and Gares[104] reported cases of Diktyoma in infants. The tumor invaded the lens capsule and lens. Malone[105] reported a case of Diktyoma that metastasized to the skull, brain, and lung. This case demonstrates the potential malignancy of a tumor that has been considered relatively benign as compared with retinoblastoma.

Negri and Rizzini[106] studied uveal melanomas by histochemical methods. The presence of a high percentage of glycogen and lipids was a constant finding that had no relationship to the pigment content. A large quantity of ribonucleic acid was present in the large polyhedral cells. Such a method of study is said to give more useful criteria for prognosis than the Wilder method.

Deen[107] made a pathologic survey of malignant melanomas of the uveal tract and reported 66 cases of his own. His cases were followed from three months to three years. Such a follow-up is entirely inadequate. A statement was made that spontaneous onset of malignant melanoma may follow intraocular inflammation. Such a situation is dangerous to document and hard to prove. Redslob reviewed the literature on melanomas through the 19th and 20th centuries.[108]

Levison[109] reported a case in which one eye was removed for malignant melanoma. Two years later metastases were diagnosed by x-ray and melanogen was present in the urine. Five months later all symptoms had disappeared. Two years later (four years after the enucleation) the patient was free

of metastases. Other cases of malignant melanoma have been recorded.[110,111] Safar[112] successfully treated melanomas of the ciliary body by means of electrosurgery. An attempt at treating a hemangioma of the choroid with diathermy was not successful.[113] Arkhangelsky[114] has been more fortunate with diathermy; he has treated iris tumors of all types with complete cures, with a follow-up of 12 years. Cysts of the iris can be successfully treated by electrolysis.[115] X-ray, in doses of less than 600 r, can cause the disappearance of spontaneous iris cysts. Such a dose of x-ray is said not to cause radiation cataract.[116] Eoche-Duval[117] demonstrated that a meningioma originating from the sphenoid ridge can extend along the optic nerve to the choroid. Donovan[118] observed a ciliary body tumor after cataract extraction. Transillumination was not interfered with. The eye was finally enucleated, and the tumor proved to be a neurilemona. The rare tumor is interesting, but the failure to interfere with transillumination further emphasizes the inaccuracy of this test.

A well-documented case of nevoxanthoendothelioma was reported by Maumanee.[119] Bronstein,[120] in his report of a case of multiple myeloma of the choroid, advanced the idea brought out by Reese and Blodi that the choroid has a hemopoietic potential.

Dunbar[121] reported a case of leiomyoma of the ciliary body that showed an increase in the uptake of radioactive iodine. This is the first such case reported.

Identification of choroidal melanomas is possible through the study of aspirated subretinal fluid. Christensen[122] considers this procedure dangerous. Andersen[123] advocates performing a biopsy through an incision in the sclera. This is even more dangerous than an aspiration. Larmande[124] was able to identify malignant cells in a punch biopsy specimen taken from an iris tumor.

An attempt was made by Bettman and Fellows[125] to identify different dark lesions of the fundus. The criteria required the same findings for small melanomas as are seen in typical large tumors.

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Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION ON OPTHALMOLOGY

Maynard C. Wheeler, Chairman
Harold W. Brown, Secretary
April 16, 1956

A Simple Operation for Senile Spastic Entropion. MARTIN BODIAN, M.D. (by invitation).

A simple operation for senile spastic entropion is described. The operation was first observed in France, where it was performed by several ophthalmic surgeons. The procedure as performed by me follows: The inferior lid is anesthetized by ballooning out the skin with 2% procaine. The incision is made 2 to 3 mm. below the inferior lid margin and runs the length of the lid. The inferior lip of the incision is undermined by means of sharp and blunt dissection, separating skin from underlying orbicularis oculi muscle. After the muscle has been isolated, it is coagulated by one of several means—diathermy, ball point, hyfrecator, or hot muscle hook. The most easily regulated and convenient of these is the diathermy current. The coagulation is applied in two parallel rows along the length of the orbicularis muscle. An elliptical strip of skin is now excised from the length of the inferior skin margin, measuring 3 to 5 mm. at its center. The skin is then closed with interrupted sutures. Antibiotic ointment and semipressure dressing complete the operation. Bed rest is not essential.

Results on 10 cases operated on with the above technique gave excellent cosmetic and functional results in 9 cases. One case had a slight amount of overcorrection, but this in no way interfered with the comfort or function of the patient's eye. I recommend the operation because of its complete simplicity and good results.

Discussion

DR. WENDELL L. HUGHES: I have listened with a great deal of interest to this very well-presented paper and feel that Dr. Bodian has made a very nice contribution. He has emphasized in the mechanics of the correction of the orbicularis some important things that I think are very pertinent. The tightening of the orbicularis I think should be particularly emphasized, and, although he did not especially mention it, he showed it in his pictures. The shortening of the orbicularis I feel should be both in the horizontal and in the vertical plane. Another thing he did not particularly emphasize is that he does produce a firm attachment of the orbicularis to the underlying lower border of the tarsus. I think that in the production of the spasm the loose attachment of the orbicularis to the underlying tarsus is an important feature.

This operation has somewhat the same general principles as the external application of the Ziegler cautery through the skin, which is sometimes used for spastic entropion and which never seems to me to be too certain in its results, because of too many variables and of the uncertainty of the application of the cautery to the particular place you want to reach. There is a direct exposure in Dr. Bodian's operation, and the cautery can be applied to the exact place where

it will do the most good. I wonder if in Dr. Bodian's one case where he had an overcorrection there was an unduly long lower lid in the horizontal direction. I would like to ask if he felt that lid was longer than would be necessary to fit the curve of the globe and if possibly that was the reason for the overcorrection. I have found in most cases in which the Wheeler procedure (i.e., the imbrication of the orbicularis) has produced an overcorrection there has been an unduly lax lid margin, in which the lower lid is too long horizontally to hug up against the globe.

I would like to ask Dr. Bodian what his postoperative care is, just how long he keeps his dressings on, and whether drops, ointments, and compresses are used.

There are a few conditions in which I think the ordinary Wheeler procedure does not do so well. I think we are concerned especially with the tarsal fibers of the orbicularis which in the upper lid are in the lid border and in the lower lid are here, overlying the lower tarsus (demonstrating on slide) as rather heavy bands, and it is these fibers that become spastic and tend to over-ride the lid margin and produce the inturning of the lid.

When you see the action of the orbicularis in a person, you can see the heavy strands of fibers shown well in this illustration with the fine vertical wrinkling of the skin here and the bunching-up of the lid tissue by these tarsal fibers of the orbicularis seen through the skin. When they become overactive and the attachment to the tarsus is loose enough, this bundle of fibers, shortening the distance between its origin and insertion, produces the over-riding of the lid margin and turning-in of the lid. When the lateral canthus is quite high, and there is an oblique position of the lower lid, a spasm of the lower lid will often produce a spastic entropion in this case, and I think the Wheeler procedure does not produce as uniformly satisfactory results. Instead of tightening the orbicularis and increasing the upward pull temporally, if the insertion of the orbicularis is lowered one will produce a better, more uniformly satisfactory result. In considering the anatomy and action of the orbicularis, it is hard to illustrate it on a flat picture—that, as well as the downward curve, there is a forward curve, so that we have this hammock swing, coming down and forwards, as well as curving downwards.

The other condition I would like to speak about is an anterior position of the orbital rim temporally, when that orbital rim is more forward than the normal orbital rim; the orbicularis, which is represented by this here, instead of having a marked forward arch for the orbicularis going back to this position, is farther forward here and is much flatter across in front of the globe. In this case the direction of the pull of the orbicularis, instead of going back 18 mm., as the average is behind the cornea, pulls in a flatter plane, as seen here, where the anterior orbital rim temporally is only 11 mm. behind the cornea. Then, because of the flatter pull of the orbicularis on the tarsus, in tightening up the orbicularis you can see that there will be less effect on the inferior border of the tarsus than when the arch is much greater. In that type of case the changing of the direction of the orbicularis, by lowering the insertion temporally, will produce more uniform results.

I think Dr. Bodian has made a very nice presentation here and has emphasized some very important points in relation to the treatment of spastic entropion.

DR. MARTIN BODIAN: I want to thank Dr. Wendell Hughes for his kind words, and I appreciate his evaluation of the procedure. I also want to thank

him for showing us some features of anatomy which certainly are enlightening to me and to all who are interested in the treatment of senile spastic entropion.

One of the questions that Dr. Hughes asked was, "Was the lid too long for the globe?" I must confess I do not know. I could pull the lid down and it would snap right back into position, but I did not try to measure its length.

He also inquired as to the postoperative care. It is simple in this type of procedure. The patient can sit out of bed from the time of operation. In 24 to 48 hours the semipressure patch which is on the eye is removed and a small strip of gauze can be placed over the inferior lid wound. The amount of edema is quite minimal, thanks to the semipressure pad. The dressing is changed daily, when fresh antibiotic ointment is applied. This treatment does not require professional help. The gut sutures will slough out in a week or two, and as soon as they do dressings may be discontinued. As to eyedrops, if there has been a purulent conjunctivitis we like to use some antibiotic, perhaps sulfacetamide or chlortetracycline (Aureomycin). Once the entropion has been eliminated, almost any of these bacteriocidal agents will work.

The Early Treatment of Orbital Floor Fractures: A Preliminary Report. BYRON SMITH, M.D.; JOHN MARQUIS CONVERSE, M.D. (by invitation), and HENRY H. SHAPIRO, M.D. (by invitation).

Facial fractures are frequent in automobile accidents. Because of the higher speed of transportation larger numbers of the fractures observed are of the comminuted variety. Those of us who treat facial fractures have noted that we see relatively fewer numbers of cases of fracture-dislocation of the zygoma and larger numbers of the comminuted type of fracture.

In reconstructing the floor of the orbit for the relief of diplopia and/or enophthalmos following depressed malunited fractures, it is frequently noted that although the rim of the orbit may be intact the thin portion of the floor posterior to the rim of the orbit is depressed.

In such cases, although the relatively solid and strong bone forming the anterior margin of the floor of the orbit is replaced in good anatomical position, posterior to these reduced fragments multiple pieces of thin bone attached to periosteum on both sides become depressed into the maxillary sinus, remaining suspended to the periosteum in a hammock-like fashion. This depression causes an increase in the size of the orbit, the probable major cause of the development of traumatic enophthalmos, because the orbital fat in a larger cavity is no longer capable of maintaining the normal degree of protrusion of the eyeball.

It has now become my custom in treating early fractures of the zygoma to verify whether I am dealing with a comminuted fracture. If there is any evidence that the fracture is more than a simple fracture-dislocation of the body of the bone, the maxillary sinus is opened through the canine fossa. It is cleansed of hematoma, and the undersurface of the floor of the orbit is examined and palpated with the tip of the finger. If examination reveals a fracture with depression, immediate measures are taken to restore the continuity of the floor of the orbit.

An incision is made in one of the skin folds of the lower lid. The skin is separated from the orbicularis oculi muscle fibers over a distance of 3 to 5 mm. along the upper margin of the skin incision. The fibers of the orbicularis oculi muscle are then split, and the margin of the fractured floor is exposed. The

periosteum of the margin is then incised, and a subperiosteal elevation of the orbital contents is undertaken. A retractor is placed along the floor of the orbit, the orbital contents are gently retracted upward, and the floor of the orbit is examined. Displaced fragments along the orbital rim are reduced, and fixation is maintained by direct interosseous wiring. If the floor is finely comminuted, a bone graft is removed from the inner aspect of the ilium and a thin plate of inner table with some cancellous bone attached is laid across, bridging the comminuted portion of the floor, thus restoring the floor of the orbit and preventing the downward displacement of the orbital contents into the maxillary sinus.

I feel that this method is a direct approach to a problem which so far has not been satisfactorily solved. Packing the maxillary sinus and placing various types of supports in order to maintain the position of the comminuted floor of the orbit lack precision, may lead to infection, and have not proved satisfactory in my hands. I feel that this method affords a direct approach and an immediate correction of the cause of traumatic enophthalmos.

(A moving picture was shown of the early restoration of the floor of the orbit by an iliac bone graft in a patient treated six days after sustaining a comminuted fracture of the orbital floor in an automobile accident.)

Discussion

DR. BENJAMIN ESTERMAN: Is there any chance of obtaining overcorrection from inserting a bone graft which is too thick, thus impinging on the orbital space?

DR. ARTHUR E. SHERMAN: I should like to know if Dr. Converse has something to say about the method of reducing depressed fractures of the orbital floor by introducing a urethral sound into the antrum through the nose, as reported by Dr. E. P. Cardwell several years ago. (Cardwell, E. P.: Fracture of the Zygomatic Tripod: Easily Reduced by Intra-Nasal Manipulation, *Plast. & Reconstruct. Surg.* 4:235, 1949). He claims that when the floor is set back in place by this method it will stay. Actually, I have not seen any of his cases that he reported on.

DR. JOHN MARTIN CONVERSE: Dr. Esterman asked whether it is possible to overcorrect in restoring the floor of the orbit. If the bone graft were to be made too large, the eyeball would protrude. In considering the role of the orbital fat in maintaining the normal degree of protrusion of the eyeball, if the same quantity of orbital fat is in an enlarged cavity, the eyeball is going to become enophthalmic; if the same amount of orbital fat is in a smaller cavity, the eyeball will become exophthalmic.

Dr. Sherman asked about the use of a urethral sound introduced through the nasal cavity into the maxillary sinus for the reduction of a depressed orbital floor fracture. Such a procedure, I believe, was first used by Lothrop, of Boston, in 1906, and, although I do not use this method myself, it is a satisfactory method of reduction. The problem in these cases, however, is not how to reduce the fracture but rather how to obtain fixation of the comminuted fragments. Whatever method you use to reduce the fracture, the problem is how are you going to hold the fragments in position. As mentioned previously, packing the maxillary sinus is not a sufficiently positive method, and I feel that the method of bridging across the defect, actually constructing a new floor with the best possible

material, a bone graft, is the only method by which it is possible to insure against the development of traumatic enophthalmos.

Exfoliation of the Capsule of the Crystalline Lens. WILFRED E. FRY, M.D., Philadelphia (by invitation).

The subject of exfoliation of the capsule of the crystalline lens has been of interest for a considerable number of years. I first became acquainted with it while a resident at the University Hospital Eye Service and was able to examine the patients that later formed the basis of the paper by Drs. Holloway and Cowan, reported before the American Ophthalmological Society in 1930. Another paper that has been reported recently on this subject is one by Dr. Theobald, and this has brought renewed interest in this subject.

The following microscopic findings illustrated one type of capsule exfoliation: There were no vacuoles noted in the capsule. The densest stain was obtained by the use of the periodic acid stain. In areas the capsule appeared to be thick and in several layers. It is felt that these could be artefacts. At many areas there were fine granules along the surface of the lens. These occurred on both the anterior and posterior lens capsule surfaces. In no areas were they bunched or in masses. They appeared to be rather scanty. The pericapsular membrane appeared deeply stained in most sections. The staining of the pericapsular membrane, however, was less deep in the areas just beneath the granular accumulations. Broken zonular fibers were evident, and granules appeared about these fibers. At places the pericapsular membrane or a superficial membrane appeared to be slightly elevated from the surface, with accumulations at or near these areas. It is felt that this represents areas of pericapsular membrane undergoing degeneration, with the possibility of granular formation. At no place was any clear unstained space detected between the areas of granular accumulation and the underlying capsule.

In summary: 1. A case is reported in which the clinical capsular exfoliation was noted by slit lamp examination in an eye with nuclear cataracts and without glaucoma.

2. These appear to occur both on the anterior and posterior capsule.

3. The pericapsular or superficial layer of the capsule appeared to stain less densely in the areas just near and beneath the granular material and suggest that, at least in this stage of the development of capsular exfoliation, the material has its origin from degenerating pericapsular membrane.

Discussion

DR. CHARLES A. PERERA: We are very grateful to Dr. Fry for calling our attention to this entity, or group of entities—exfoliation of the lens capsule—and for the two cases which he reported with the beautiful slides showing the histologic and pathologic preparations. This subject of exfoliation of the lens capsule is an interesting one, and we would probably see more cases if we routinely enlarged the pupil of all middle-aged and elderly patients and studied them with the slit lamp. It is likely that we would not see a large number of cases, perhaps in an active practice anywhere from three to six cases a year.

There is a distinct relationship between exfoliation of the lens capsule and senile cataract and glaucoma. I wish to report an interesting case in which the condition occurred unilaterally in an old patient. The patient, now 79, was seen

five years ago by Dr. Bassen, who discovered in one eye granular exfoliation of the anterior lens capsule outside the pupillary area, with increased intraocular pressure. The patient was put on pilocarpine, 2% three times a day, and the intraocular pressure has remained within the limits of 25 to 35 since that time. Study with the gonioscope showed an open angle in the left glaucomatous eye, with exfoliation of the lens capsule and some granules, with a very few on the surface of the iris. During the five years that have passed, the lens on the side of the exfoliation has become more and more opaque, whereas the lens without exfoliation has remained fairly transparent, with a vision of 20/25. The question arose as to whether anything should be done in view of the low-grade glaucoma and in view of the progressive loss of nasal field in the left eye. The patient was a highly neurotic one and had sought other opinions about removing the cataract. Dr. Bassen and I were conservative about doing anything. The patient went to see Dr. Dunnington, who gave the sound and conservative advice to leave the condition alone. Since then the patient has been happy, and the eye has been left alone. This is the second case I have seen with unilateral exfoliation of the lens capsule, but the other case did not have glaucoma.

News and Comment

ANNOUNCEMENTS

Certificate in Ophthalmic Surgery.—The present certificate of the American Board of Ophthalmology gives no indication of a specialist's surgical ability. It merely indicates that he is familiar with the principles of surgery. This has been necessary because many outstanding ophthalmologists do not perform surgery. In addition, in some instances the specialist has received excellent training in ophthalmology but with little opportunity to develop surgery.

It is for this reason that the Board has decided to set up an examination for certification in ophthalmic surgery.

The preliminary requirements and the plan of examination follow.

Preliminary Requirements.—1. Possession of a certificate of the American Board of Ophthalmology for a minimum period of three years.

2. Ethical standards complying with the principles of ethics of the American Medical Association and the candidate's county or local Medical Society.

3. The candidate shall submit a certified list of 200 major operations; this is to include 90 cataract operations, 46 muscle operations, 24 glaucoma operations, and 40 major operations including retinal detachment, diseases of the lacrimal apparatus, traumatic surgery, and plastic reconstruction. All of the above operations are to have been performed after the candidate has been certified in ophthalmology. In special instances the Board may alter the specified number of the various listed operative procedures but without decreasing the total number of cases.

4. The candidate shall submit with his application reports of 30 cases of diversified major surgery that he has performed since certification by the Board. These case reports are to include 15 cataract operations, 6 muscle operations, 3 glaucoma operations, and 6 additional major procedures of various types. These case reports should include preoperative work-up and notes, a certified copy of the hospital record; postoperative notes, a certified copy of the pathology report if present. All data submitted are to be typed with double spacing, and the case reports are to be in duplicate.

5. All faculty members who have practiced for 20 years and who perform surgery and who have professorial rank in ophthalmology in Grade A Medical Schools shall be invited to take the written examination, and upon passing the examination and upon payment of the fee they shall be issued the certificate in Ophthalmic Surgery.

Case reports will not be required in this group. This regulation is to be in effect for a period of three years following the adoption of these regulations.

6. Candidates who have completed their training in an approved residency program shall present to the Board a statement from the candidate's supervising surgeon, or surgeons, during his training time, vouching for the candidate's integrity, surgical judgment, and technical skill as shown during his training period. In the event that this is not possible, the candidate should present letters from three certified ophthalmic surgeons who are familiar with his work. These letters are to be sent directly to the Secretary of the Board.

7. Candidates who have not had a recognized residency but who present evidence of otherwise meeting the requirements may be admitted to examination upon the Board's receiving a satisfactory letter from the candidate's preceptor, who must be a certified Ophthalmic Surgeon.

8. Letters are to be requested by the Secretary from three certified ophthalmic surgeons who reside in the candidate's community, or vicinity, stating the candidate's surgical ability, judgment, and integrity as observed by them. These letters are to be sent directly to the Secretary of the Board.

These letters may be from certified ophthalmologists as well as Ophthalmic Surgeons until the list of Ophthalmic Surgeons is adequate.

Examination.—Upon fulfillment of the above requirements, the candidate will be eligible for examination, which is divided into two parts:

1. Written Examination: This will be a comprehensive written examination, covering (*a*) surgical principles; (*b*) anesthesia, both local and general, together with knowledge of the care of complications arising from anesthesia; (*c*) indications for surgery; (*d*) preoperative and postoperative care, and (*e*) surgical complications and their care.

2. Practical Examination: A. One part of the examination shall consist of the candidate's observing patients with surgical conditions, followed by discussion of and quizzing on the diagnosis, management, procedure, and possible complications immediately postoperatively and at a later period. This examination is to be based on the patients examined.

B. Another part of the examination is to consist of a discussion and quiz based on the candidate's list of surgical case reports of patients operated upon since his certification.

Fee.—A fee of $150.00 is payable with the application and is not returnable if the candidate fails in the written examination. The fee for reexamination is to be $100.00.

Certification.—Upon completion of the examination the candidate will receive a certificate from the American Board of Ophthalmology stating that he has successfully passed the examination in Ophthalmic Surgery.

In order to establish the examination, it is necessary that a group of certified ophthalmic surgeons be established. To accomplish this, a special committee has been set up composed of former Board members interested in surgery. This group, which includes some of our most outstanding ophthalmic surgeons, will be certified without examination. This special committee is to give the examination to those active Board members desiring surgical certification. The examination is to consist of a written examination. These examination papers will be anonymous, being identified by a number known only to the registrar of the Board.

In this manner the Board will create a sufficient number of certified ophthalmic surgeons to start conducting the examination.

Plans for the organization of the examination are now under way, and it is hoped that the first examination can be given in January, 1958, at the time of the written examination given for regular certification by the Board.

Sectional Meeting of Association for Research in Ophthalmology.—The next Sectional Meeting of the Association for Research in Ophthalmology will be held at the Kresge Eye Institute, in Detroit, on Monday, Jan. 7.

Dr. A. D. Ruedemann has been appointed chairman of the meeting and is issuing a call for abstracts of papers to be submitted. Dr. Kinsey has already received abstracts of several, but there will be an opportunity for many more presentations. Papers should be based on pure research and be nonclinical. Approximately fifteen minutes will be allowed for each paper. Abstracts must be in the form of summaries, be triple-spaced, and be written in a form suitable for printing without further editing.

Please send abstracts as soon as possible to A. D. Ruedemann, M.D., Kresge Eye Institute, 690 Mullett St., Detroit 26.

Seven Medical Scientists, Two Groups Win 1956 Albert Lasker Awards.—Seven scientists and two health groups were presented with the 1956 Albert Lasker Awards of the American Public Health Association at Atlantic City, N. J., Nov. 15.

Ranked among the nation's highest medical honors, the awards were conferred at the Association's eighty-fourth annual meeting in the Hotel Ambassador by Dr. Gaylord W. Anderson, chairman of the Lasker Awards Committee and director of the School of Public Health, University of Minnesota.

Two of the 1956 winners are Dr. V. Everett Kinsey, assistant director of research, Kresge Eye Institute, Detroit, and Dr. Arnall Patz, ophthalmologist, Baltimore, Md., who were presented a joint award, for "distinguished achievement in discovering excessive oxygen administration to be the cause of retrolental fibroplasia (blindness) in prematurely born babies."

Dr. Kinsey and Dr. Patz have pursued original well-controlled studies in the cause and prevention of retrolental fibroplasia in prematurely born babies. As a physician in private practice, Dr. Patz used his own resources to ascertain for the first time that "routine high oxygen levels" were the cause of blindness in many of these infants. Dr. Kinsey subsequently "coordinated an investigation involving 18 hospitals and 75 ophthalmologists and pediatricians which produced conclusive and definitive proof of the relation between high oxygen concentrations and this blinding condition." In the U. S. alone, the results of this research should prevent blindness in several hundred prematurely born infants each year.

Seventh International Cancer Congress.—The Seventh International Cancer Congress, sponsored by the International Union Against Cancer, will be held in London, England, July 6-12, 1958, under the presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress: (*a*) experimental and (*b*) clinical and cancer control.

Special emphasis will be placed on hormones and cancer, chemotherapy, carcinogenesis, and cancer of the lung.

Proferred papers will be considered only if submitted with an accompanying abstract (not over 200 words) before October, 1957, and if they deal with new and unpublished work.

The registration fee for the Congress will be £10, or $30, and the latest date for registration without late fee will be Jan. 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to The Secretary General, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W. C. 2.

Postgraduate Ophthalmology Course.—Ohio State University, Columbus, announces a Postgraduate Course in Ophthalmology to be held in the Ohio State Union Building Conference Theater, on the University campus, March 4-5, 1957.

Speakers will be Francis H. Adler, M.D., University of Pennsylvania; George J. Hamwi, M.D., Ohio State University; John W. Henderson, M.D., University of Michigan; William E. Hunt, M.D., Ohio State University; Jay Jacoby, M.D., Ohio State University; Alfred E. Maumenee, M.D., John Hopkins University, and Ted Suie, Ph.D., Ohio State University.

The registration fee is $20.00. Registration by mail is desirable. Address all inquiries to William H. Havener, M.D., Department of Ophthalmology, University Hospital, Columbus, Ohio.

Stanford Postgraduate Conference in Ophthalmology.—Stanford University School of Medicine will present the annual postgraduate conference in Ophthalmology from March 18 through March 22, 1957. Registration will be open to physicians who limit their practice to the treatment of diseases of the

eye or to the eye, ear, nose, and throat. In order to allow free discussion by members of the conference, registration will be limited to thirty physicians.

Instructors will be Drs. David L. Bassett, Jerome W. Bettman, Max Fine, Earle H. McBain, Arthur J. Jampolsky, and Dohrmann K. Pischel.

Programs and further information may be obtained from the Office of the Dean, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15.

The XVIIIth International Ophthalmological Congress.—The first International ophthalmological Congress was held in Brussels in 1857. On the occasion of this centenary, the next congress will be held also in Brussels, Sept. 8 to 12, 1958, under the presidency of Prof. Léon Coppez.

All ophthalmologists are cordially invited to attend, and we trust that a great number will come to Belgium, where that same year a great Universal International Exhibition will be taking place.

The following main subjects have been chosen by the International Council:

1. Orthoptic treatment of concomitant strabismus, which will be presented by Dr. A. Bangerter (St.-Gallen); Dr. T. K. Lyle (London), and Prof. J. Malbran (Buenos-Aires).

2. Geriatrics in Ophthalmology, which will be presented by Prof. M. Buerger (Leipzig); Prof. J. François (Ghent); Prof. G. Jayle (Marseilles), and Prof. M. Jayle (Paris).

Symposia will be organised on cataract, radioisotopes in ophthalmology, electroretinography, and glaucoma.

Sessions will be reserved for free communications.

The International Association for Prevention of Blindness and the International Organization Against Trachoma will hold meetings during the Congress.

All correspondence and requests for information should be sent to the General Secretary, Prof. Jules François, 15, place de Smet de Naeyer, Gand (Belgique).

Harvard Medical School Postgraduate Courses.—For the fourteenth consecutive year, the Harvard Medical School offers the postgraduate courses Basic Sciences in Ophthalmology, Sept. 23, 1957, to Jan. 16, 1958, and Introduction to Clinical Ophthalmology, Jan. 17 to March 7, 1958.

Inquiries should be addressed to Assistant Dean, Courses for Graduates, 25 more, on April 27, 1957.
Shattuck St., Boston 15.

Eastern Section, Association For Research in Ophthalmology.—The next meeting of the Eastern Section of the Association for Research in Ophthalmology will be held at the Wilmer Institute of The Johns Hopkins Hospital, in Balti-

Anyone wishing to present a paper before the Section is urged to communicate with Dr. Howard Naquin, The Johns Hopkins Hospital, Baltimore 5, as soon as possible. Speakers will be limited to a maximum of fifteen minutes. Papers can be presented at the Eastern Section Meeting as well as at the national meeting in New York City in June.

British Columbia Oto-Ophthalmological Conference.—The British Columbia Oto-Ophthalmological Conference will be held in Vancouver, B. C., on May 23 and 24, 1957. Guest speakers will be Dr. Alston Callahan, Birmingham, Ala., in ophthalmology, and Sir Victor Negus, London, England, in otolaryngology. Members of neighboring eye, ear, nose, and throat societies are cordially invited to attend.

Books

Transactions of the American Ophthalmological Society, 1955: Vol. 53. Price, $18.00. Pp. 522. Columbia University Press, 2960 Broadway, New York 27, 1955.

The papers appearing in the 91st annual meeting of the American Ophthalmological Society are as follows:

The Importance of Ophthalmoscopic Photographs in Forensic Medicine: Kodachromes

Arthur J. Bedell, M.D.

Atrophy of the Stroma of the Iris, Endothelial Dystrophy, Corneal Edema and Glaucoma

Paul A. Chandler, M.D.

Some Semiautomatic and Automatic Trephines, Including an Electric Trephine with Automatically Retracting Blade

F. H. Verhoeff, M.D.

Permanent Bilateral Blindness Following the Use of Hexamethonium Chloride

Gordon M. Bruce, M.D.

Absence of the Medial Rectus and Its Successful Treatment by Vertical Tendon Transplants

Howard F. Hill, M.D.

Results of a Combination Operation for Cataract with Glaucoma

Wendell L. Hughes, M.D.

Periorbital Fibrous Dysplasia

Ralph O. Rychener, M.D., and (by invitation) Francis Murphey, M.D.

Use of Carbonic Anhydrase Inhibitor Acetazoleamide (Diamox) for Endothelial Corneal Dystrophy and Diseased Corneal Grafts

Frederick W. Stocker, M.D.

A Safe Section for Cataract Extraction

Walter S. Atkinson, M.D.

A Comparative Study of Gonioscopic Methods

Robert N. Shaffer, M.D., and (by invitation) Robert L. Tour, M.D.

Glial Tumors of the Retina in Relation to Tuberous Sclerosis

John M. McLean, M.D.

Myopia Caused by Prematurity

Henry L. Birge, M.D.

Some Causes of Enucleation after Cataract Extraction

Brittain F. Payne, M.D., and (by invitation) John T. Simonton, M.D., and Dahar Cury, M.D.

Hereditary Congenital Ophthalmoplegia

William John Holmes, M.D.

Paredrine Hydrobromide: Intraocular Pressure Evaluations

F. L. Philip Koch, M.D., and (by invitation) Louise H. Darley and Paul Levatin, M.D.

Tonography in the Clinical Management of Glaucoma
Harold G. Scheie, M.D., and (by invitation) Robert W. Spencer, M.D., and Ernest D. Helmick, M.D.

Aqueous Pathways in Some Cases of Glaucoma
Georgiana Dvorak-Theobald, M.D., and (by invitation) Harold Quentin Kirk, M.D.

Corneoscleral Lesions in Periarteritis Nodosa and Wegener's Granulomatosis
David G. Cogan, M.D.

Fluorescent Materials for Orthoptic Training
Lester H. Quinn, M.D.

The Transactions also includes the following theses, accepted for membership in the Society:

Intracranial Arterial Aneurysms: A Study of 119 Cases, with Special Reference to the Ocular Findings
John Woodworth Henderson, M.D.

Tonometry and the Cornea
J. W. Jervey Jr., M.D.

Reactions of the Iris to Injury
Albert C. Snell Jr., M.D.

Advances in Ophthalmology: Volume V. Edited by E. B. Streiff. Price, SF 39.50. Pp. 293. S. Karger AG, Arnold Böcklinstrasse 25, Basel, Switzerland, 1956.

The papers appearing in the fifth volume are as follows: Lesions uveales et vasculaires retiniennes précoces dans l'infection tuberculeuse, by R. Dufour, Lausanne; Cytological Aspects of the Crystalline Lens: A Critical Review and an Outlook on Future Development, by J. E. A. VanDenHeuvel, Groningen; Uvee (1re Partie) Annes 1946-1953, by J. François et E. DeVos, Gand.

Advances in Ophthalmology: Volume VI. Edited by E. B. Streiff. Price SF 48.00. Pp. 372. S. Karger AG, Arnold Böcklinstrasse 25, Basel, Switzerland, 1956.

Volume VI contains the following original papers: Über die Keratoplastik mit Paraffinmaterial: Ein Beitrag zur Frage der Hornhautkonservierung, by E. Burki, Basel; Bewegungsapparat der Augen, 1947-1952, by P. A. Jaensch, Essen; Cornée et sclérotique (Revue de la littérature de 1946 à 1951) (2me Partie), by S. Forni, Genève.

The index, Volumes I to VI, inclusive, is included in this volume.

Stereoscopic Atlas of Human Anatomy: Section III. The Upper Extremity. By David Lee Bassett, M.D. Price, $22.50. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

The third section of this excellent stereoscopic atlas of human anatomy concerns a dissection of the upper extremity. This will be of little interest to ophthalmologists, but it continues to provide those interested in the visual presentation of anatomical data with an excellent atlas.

The Boxer. By Daniel M. Gordon, M.D. Sixth edition. Price, not given. Judy Publishing Company, 3323 Michigan Blvd., Chicago 16, 1956.

It has been said that every doctor should have a hobby, and Dr. Dan Gordon of New York City is a good example of this. A true dog-lover, he has for many years been interested in the Boxer, having owned and bred several champions. Sixteen years ago he brought out his first book on this breed. This year he

presents the sixth edition, which is a complete description of the origin, development, breeding, showing, training, kenneling, and feeding of the Boxer.

In addition, there is a general dog manual which applies to dogs of any breed. Although not written from the viewpoint of the veterinarian, there is a short chapter on the common diseases of the dog and first-aid measures, including a paragraph on the eyes!

The book is profusely illustrated not only with good photographs and amusing cartoons but also anatomical drawings. It is recommended for those who own dogs.

Veterinary Ophthalmology. By R. H. Smythe. Price, $7.50. Pp. 356 with 50 illustrations. Ballière, Tindall & Cox, 7-8 Henrietta St., Covent Garden, London W. C. 2, 1956.

This text is intended for veterinarians and students of veterinary medicine, but as usual there is much to learn from the diseases of animals' eyes which has application to the theory and practice of ophthalmology in human beings.

Part I describes the anatomy and physiology of the eye. Most of this is adequately done, although there are sections where the author has fallen badly behind the times, as when he quotes Duke-Elder, "There is no conclusive or indeed persuasive evidence that the intraocular fluid is a secretion" (Duke-Elder, S., and others: *Brit. J. Ophth.* 24:421, 1940). Further, he seems to have limited his reading largely to the writings of Thompson-Henderson, who, while he always writes in a stimulating fashion, has not always been accepted as drawing the correct conclusions.

Part II is the usual treatment of methods of clinical examination of the eye, the diseases which affect animals' eyes, and their treatment. True glaucoma occurs in dogs and monkeys, while secondary glaucoma sometimes follows periodic ophthalmia in horses. Operation is apparently disappointing, and the eyes usually become blind.

Many of us are called on by our friends to treat their pet dogs and cats, and this little book will be found very serviceable to have tucked away in a corner for such emergencies. It is well recommended.

Textbook of Orthoptics. By H. W. Gibson. Price, 42 shillings. Pp. 449, with illustrations. Hatton Press, Ltd., 72-78 Fleet St., London, E. C. 4, 1956.

The author of this book is the senior staff orthoptist and lecturer in orthoptics at the London Refraction Hospital. He is the author of a previous book, "Clinical Orthoptics," which is now out of print. The book is well written and well illustrated. It covers the anatomy and physiology of the ocular muscles. There are good chapters on heterophoria and on all of the clinical aspects of strabismus, both comitant and incomitant.

The author seems to be fully aware that orthoptic treatment has its limitations, and the chapters on treatment will serve as an excellent manual for all orthoptists.

Surgery of the Eye: Diseases. By Alston Callahan, B.A., M.S. (Ophth.), M.D., F.A.C.S. Price, $25.00. Pp. 447, with 263 illustrations including 19 colored. Charles C Thomas, Publisher, 301-327 Lawrence Ave., Springfield, Ill., 1956.

In this comprehensive volume the author has covered the vast majority of the surgical conditions which the ophthalmologist will encounter. The subject matter has been presented in a most readable form. The illustrations are outstanding for their excellence and clarity of portrayal. The printing is also of the highest order. These features along with the author's concise style of writing make this book one that every ophthalmic surgeon should possess.

In the chapter on anesthesia proper emphasis is placed upon individualization of dosage and the dangers of oversedation. The next five chapters are devoted to the surgical treatment of various lid conditions. In these pages one finds excellent descriptions of many of the less common types of operative pro-

cedures. On occasions the author gives several techniques for the correction of the problem at hand, thus enhancing the reference value of this volume. The usual intraocular operations are similarly dealt with, and in the chapter on cataract extraction the techniques employed by various surgeons are described and amply illustrated. The operative and postoperative complications of cataract extraction are discussed in a lucid manner, although in some minor details the views expressed are at variance with the generally accepted opinion. The classical operations for glaucoma are described in some detail after a preliminary discussion of the preoperative management of this disease. The surgical treatment of detachment of the retina is incompletely covered, for the author only gives the method he uses and states that it is "not feasible to describe the considerable number of successful variations in technic employed by many ophthalmic surgeons." The chapters on ocular muscle surgery and enucleation, which are adequate, are followed by an excellent presentation on surgery of the orbit.

In a short appendix the author outlines in a succinct manner the management of ocular injuries.

From this volume much can be learned of the operative techniques not only of the author but also of other surgeons, for they are clearly described and beautifully illustrated. This book fills a most important need in ophthalmic literature.

The Complete Medical Guide. By Benjamin F. Williams, M.D. Price, $4.95. Pp. 913. Simon and Schuster, Inc., 630 Fifth Ave., Rockefeller Center, New York 20, 1956.

The increased interest of the public in medical affairs is attested to by the large number of television programs on medical subjects, ranging from simple expositions of medical facts by experts to lurid dramas emphasizing the emotional impact of medicine on both patient and doctor.

As an accompaniment to these visual presentations of medicine to the public we have an increasing number of medical books written for the laity, of which this is the latest. There is no doubt that it is a good sign that the public is taking an interest in medicine and is becoming more intelligent about disease and its treatment. It is, therefore, especially valuable to have books of this character written by intelligent, discriminating physicians who have the knack of making complex subjects relatively simple. Dr. Miller has done this extremely well, and no physician should worry that this book will give his patients either misinformation or just that little bit of knowledge which is a dangerous thing.

The section on eyes is regrettably small, but it is well done. The author makes a plea for all patients to see an ophthalmologist every three years if the patient is between 25 and 50, and every year after that age. Some of his suggested treatments for home care are outmoded, and even questionably good practice, as his advice to use yellow oxide of mercury ophthalmic ointment in pinkeye, or penicillin ophthalmic ointments, but on the whole his advice is sound. He emphasizes that babies with strabismus do not outgrow it and that the child should be taken at once to a physician. In future editions of this book the author should be asked to change one sentence for clarification: He states "Always have an eye doctor examine your eyes and prescribe the proper lenses." For clarification this should read "eye physician (ophthalmologist)."

Biochemistry of the Eye. By Antoinette Pirie, M.A., Ph.D., and Ruth Van Heyningen, M.A., D.Phil. Price, $7.00. Pp. 323. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

The book deals with the biochemical aspects of the eye and is a welcome and much-needed addition to ophthalmic literature. Four chapters out of ten are devoted to the lens; in them are discussed its components and metabolism, the transport of substances into and out of the organ, and experimental and senile cataracts. Other chapters deal with the cornea, the chemical aspects of vision, the retina, the vitreous body, the aqueous humor and the ciliary body, and

ocular effects of nutritional diseases. There are helpful statements on the embryological origin of certain tissues, and some of the chapters contain a lucid and critical evaluation of the present knowledge of the subject discussed. A glossary of ophthalmologic and other terms concludes the volume. The book is well documented, with references at the end of each chapter, some of which are as recent as to include publications in 1955.

Generally speaking, the authors stress those aspects of ocular biochemistry which are more familiar to them and of which they speak with considerable authority. The chapter on experimental and senile cataract might be cited as an outstanding example. The treatment of aqueous humor, on the other hand, is very brief, although the chemistry of the fluid is at least as well understood as that of the lens. This the authors take into consideration by giving adequate references to other texts and reviews in which the subject has been expertly treated. Nevertheless, this unequal partitioning of the subject matter lessens the value of the book as a general text.

It is true, as the authors say, that our knowledge of the chemistry of the sclera, the conjunctiva, and the choroid is limited, but the title of the book seems to call for some treatment of these subjects. The reviewer would also like to suggest that subsequent editions include a chapter on the lacrimal apparatus.

The authors are to be congratulated on having given a thorough representation of the biochemical processes which are known to or presumed to occur in the eye. The book is well written and easily readable. It is of particular value to the reader untrained in biochemistry because much material in basic chemistry, together with formulas, is included. The experienced ophthalmic chemist will find it a useful reference work. Moreover, the book should be of considerable interest to the clinical ophthalmologist who seeks to correlate the clinical aspects of ophthalmology with biochemical processes.

News and Comment

ANNOUNCEMENTS

Special Course for Latin Americans.—A special course in Practical Histopathology of the Eye will be offered visiting Latin American ophthalmologists at Weeks Hall, New York Eye and Ear Infirmary, 218 Second Ave., New York, April 5 and 6, 1957. The lectures will be given without charge to certified students of ophthalmology from Latin America.

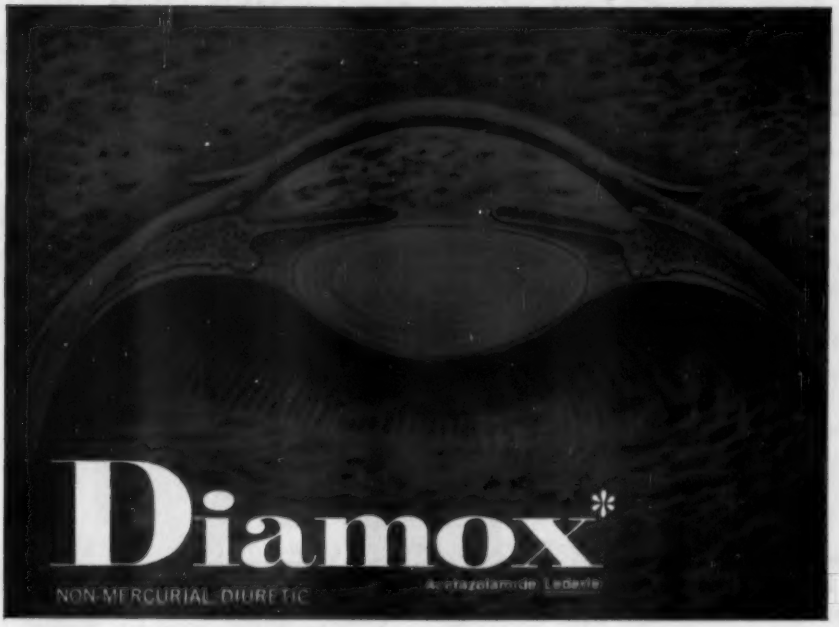
The program of the course is as follows:

Friday, April 5, 2 p. m.-5 p. m.: Normal Histopathology and Applied Microanatomy of the Ocular Globe. Drs. Brittain F. Payne and John Finley, assisted by Dr. Emanuel Almeda.

Saturday, April 6, 9-10 a. m.: Surgical Pathology. Dr. Emanuel Almeda.

Saturday, April 6, 10 a. m.-12 noon: Intraocular Tumors and Diseases of the Choroid. Dr. Lawrence Samuels.

Saturday, April 6, 1-3 p. m.: Granulomas of the Eye. Secondary Glaucoma. Dr. Bernard Roberts.



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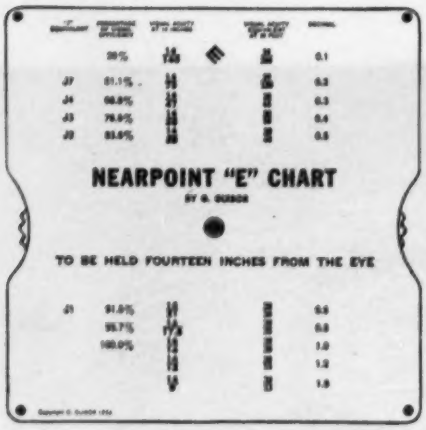

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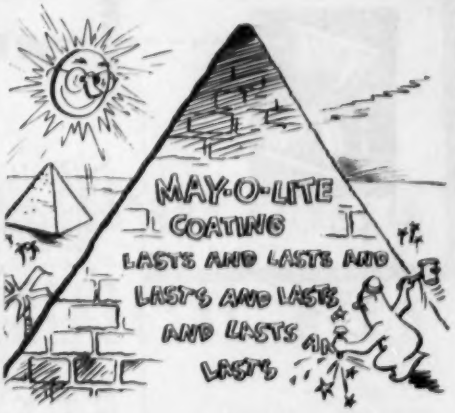

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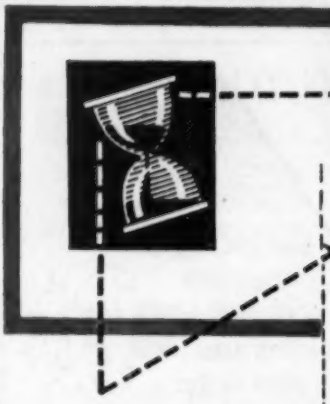

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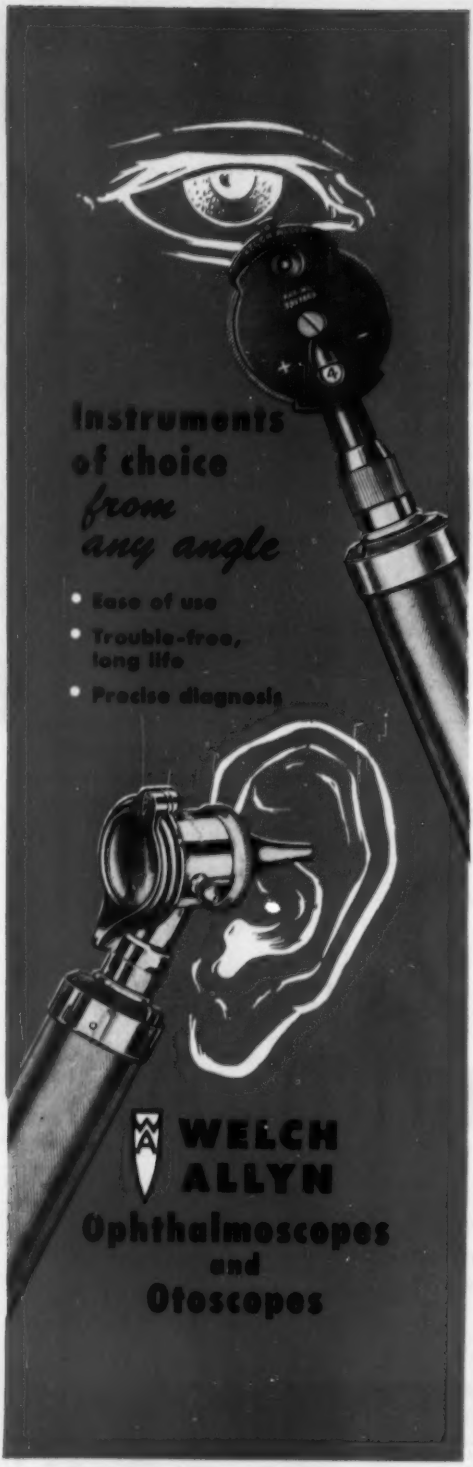

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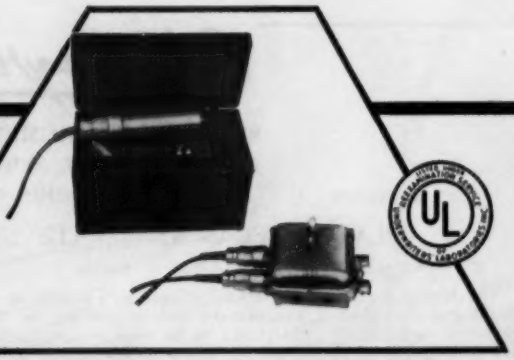

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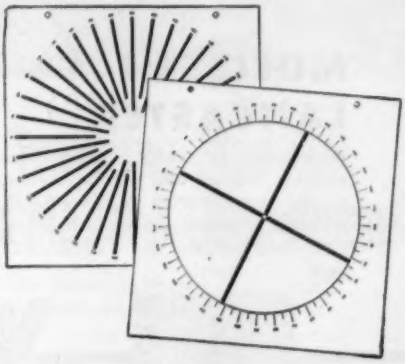

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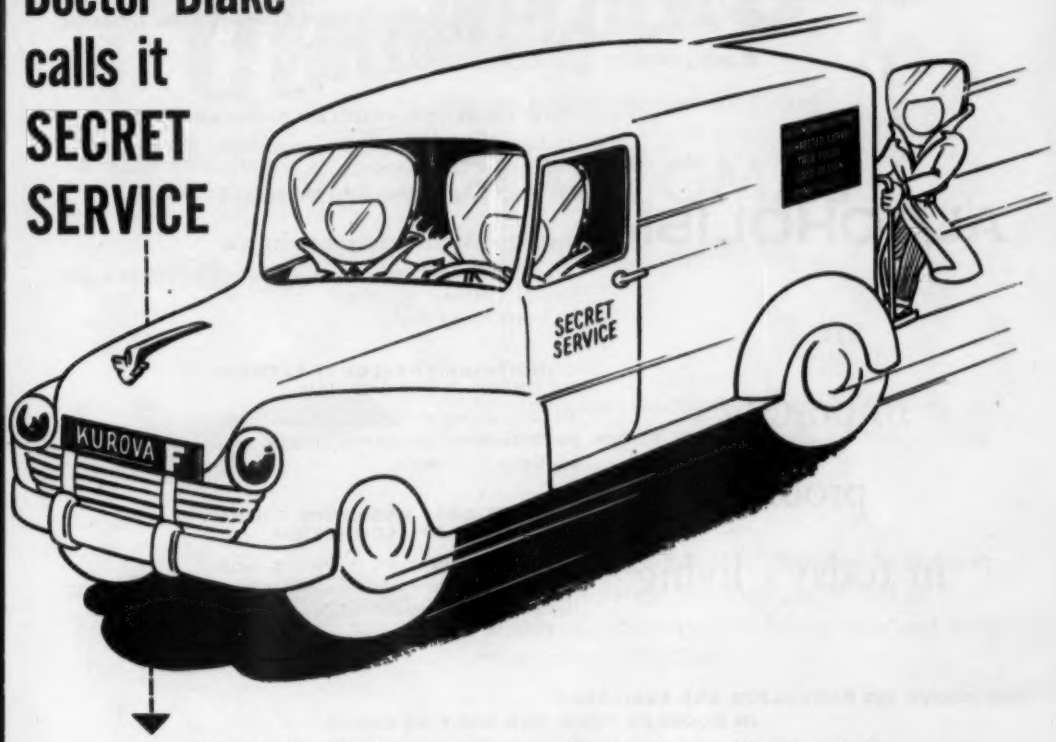

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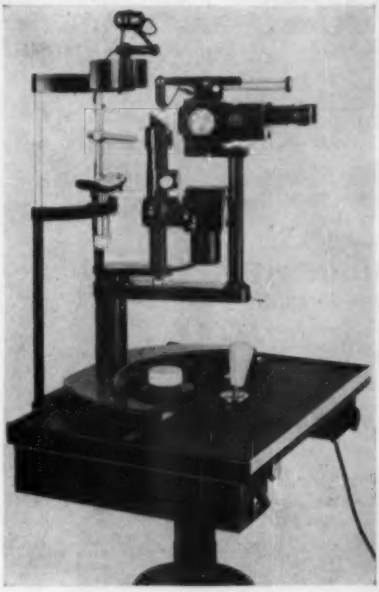

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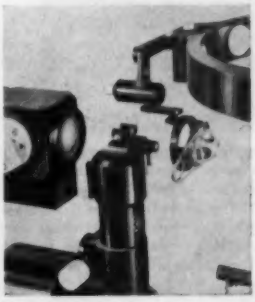

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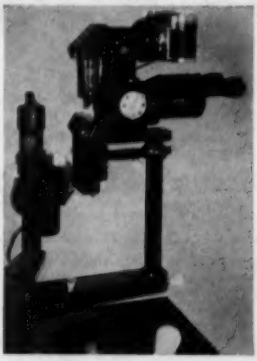

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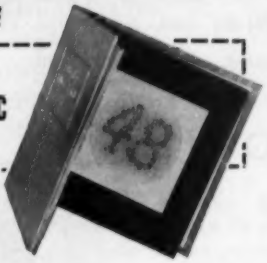

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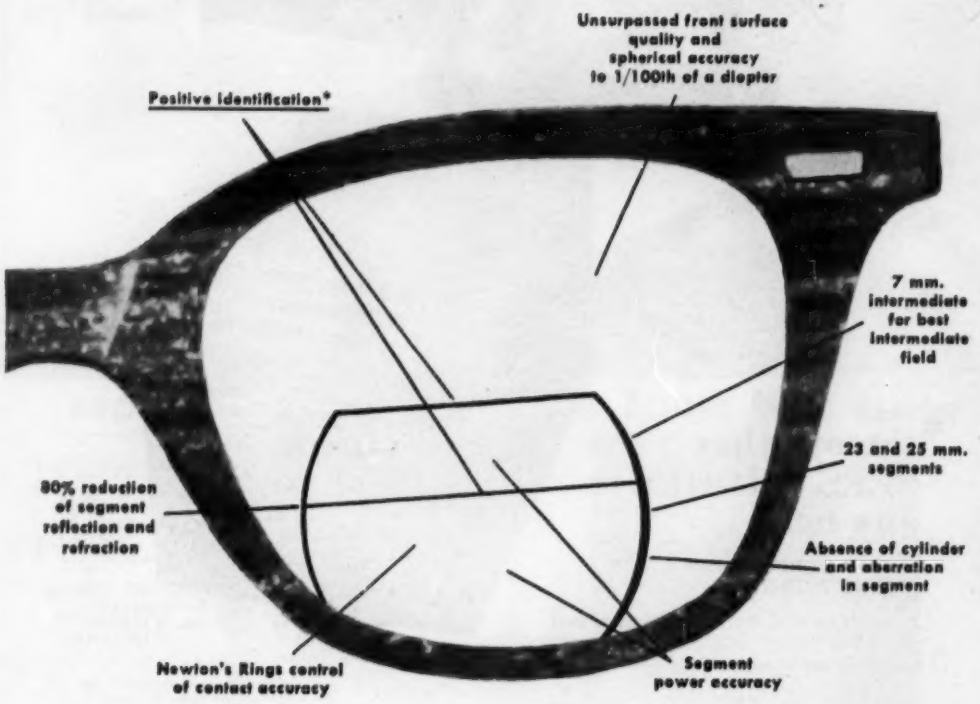
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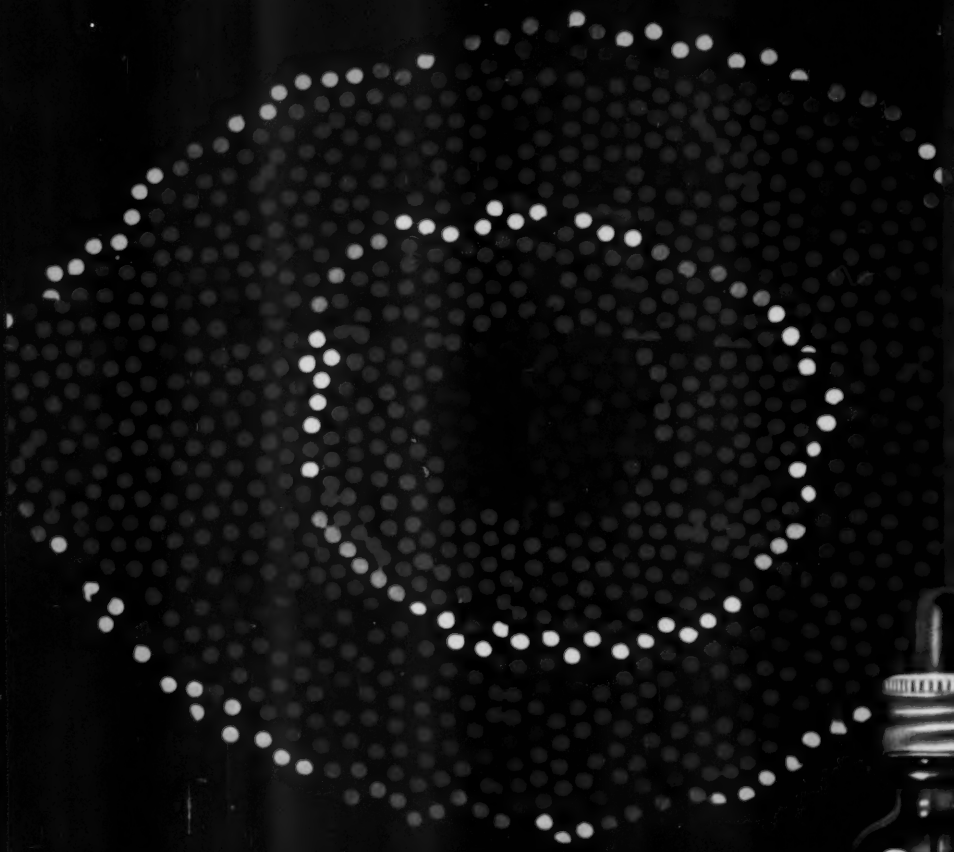

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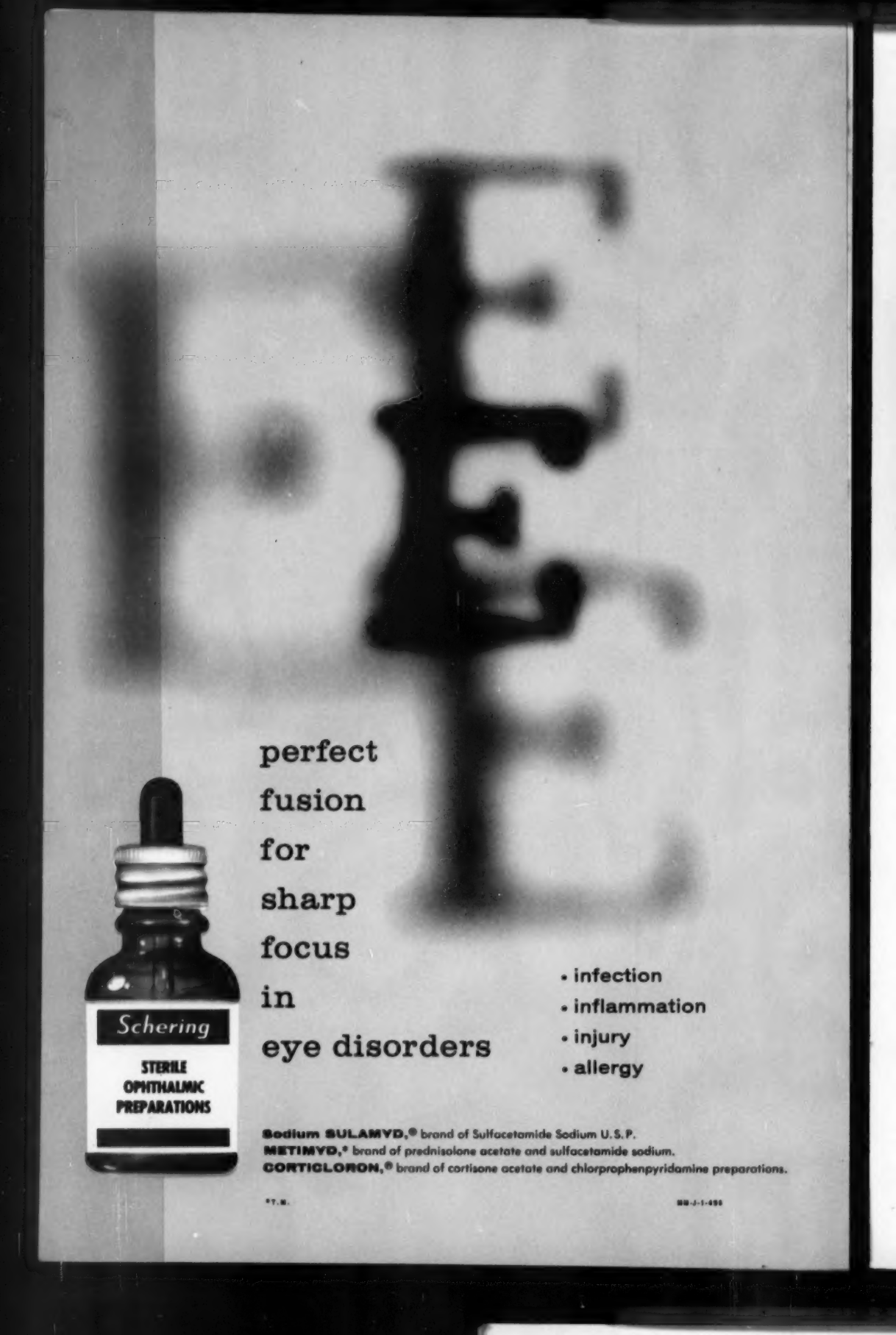
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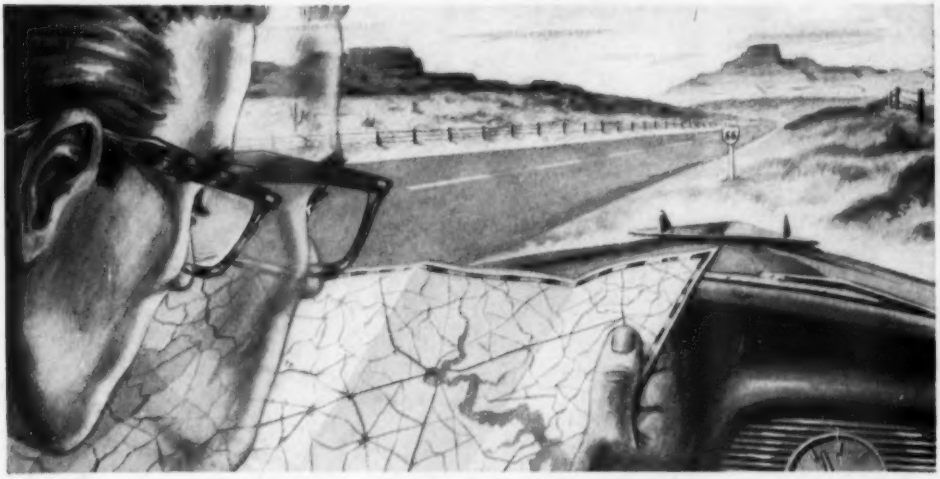

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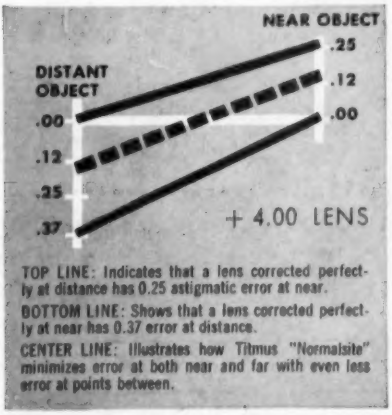

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